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METHODS FOR PRESERVATION AND TRANSPLANTATION OF ARTERIAL GRAFTS

Observations on Arterial Grafts in Dogs. Report of Transplantation of Preserved Arterial Grafts in 9 Human Cases

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IN certain operative procedures it would be of great value to be able to bridge an arterial defect with a graft, provided the method of grafting is reliable and is not cumbersome. Vein grafts (from the same individual and from other humans) have been used with some success, and are reasonably satisfactory if one is repairing arteries which are not of great size. There has been no safe method for permanently replacing a segment of a very large artery, especially the aorta, and it is to this problem that we have turned our attention.

Veins and arteries have been grafted into animals from the same animal (autografts), from the same species (homografts), and from other species (heterografts) (1, 3, 4, 5, 6, 8, 9, 13, 14, 18, 26, 31, 32, 33). It has been generally reported that autografts or homografts are more satisfactory than heterografts (5, 6, 8, 9, 14, 15). Many substitutes for blood vessels have been suggested. Various inert substances have been suggested or tried for bridging blood vessel defects (10, 11, 23), including tubes of glass, of aluminum, of gold plate, and of silver lined with paraffin. All of these substances have led to thrombosis. Recently, lucite channels for intubation of vessels (19) has led to more promising results. Rigid rings (vein lined) for the nonsuture method of joining vessels have been made from ivory (25), magnesium (28), and vitallium (1).

A wholly satisfactory solution to the problem of bridging a gap in large arteries or in the aorta would seem to lie in the direction of providing a vascular graft which is viable, which would resemble the normal vessel after implantation, which could withstand intra-arterial pressures, which would not cause thrombosis, and which would not set up serious reaction in the regional tissues. Knowing that transplantation of fresh arterial grafts from one animal to another had shown varying degrees of survival in the hands of Carrel and Guthrie (6, 8, 14) and others (3, 18, 31), we undertook to repeat and extend some of their work, and to investigate extensively methods for preservation and storage of arterial grafts. As a preliminary part of our investigations, a study was made of the effects of transplantation of fresh aorta from one dog to another; this is being reported elsewhere by Gross and Hurwitt (13).

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TABLE I.—RESULTS OF IMPLANTATION OF HOMOGRAFTS (PRESERVED BY QUICK FREEZING TO −72 DEGREES C.) INTO DOG AORTAS

Recipient dog No.	Atmosphere in storage tube	Length of time vessel preserved	Length of life of dog post-operatively	Cause of death	Fate of graft
135–47	Air	7 days	5 days	Hemorrhage	Graft broke down
136–47	Air	8 days	5 days	Hemorrhage	Graft broke down and completely thrombosed
137–47	Air	13 days	30 days	Hemorrhage	Graft broke down
139–47	Air	15 days	7 days	Hemorrhage	Graft broke down and completely thrombosed
122–47	Air	33 days	6 months	Sacrificed	Intimal sclerosis
124–47	Air	35 days	8 days	Hemorrhage	Graft broke down
125–47	Air	36 days	5 days	Hemorrhage	Graft broke down. Two thrombi
173–47	Helium	2 days	20 days	Hemorrhage	Graft broke down. Some thrombosis
174–47	Helium	3 days	19 days	Pneumonia	Tubular mural thrombus 2.0 mm. thick
166–47	Helium	7 days	8 days	Hemorrhage	Graft broke down and completely thrombosed
168–47	Helium	8 days	12 days	Hemorrhage	Graft broke down
180–47	Helium	14 days	6 months	(Still alive)	Considerable mural thrombus by aortogram

Preservation of blood vessels has been studied previously by other surgeons. Carrel (7, 9) preserved arteries by storage in a refrigerator at temperatures above freezing, in various media, including vaseline, salt solution, defibrinated blood, and humid air. With these methods he had some degree of success in survival of the grafts following their implantation into other dogs. His results are rather difficult to evaluate because of the relatively few experiments in each method of study. Recently Blakemore and Lord (1) and also Hufnagel (20) have reported the successful preservation of arteries and veins by quick freezing and storage at temperatures well below freezing. The successful transplantation of an artery after preservation in formalin was reported by Levin and Larkin (21, 22), but they were apparently unable to repeat this in later experiments. This was later successfully repeated by Guthrie (16).

Based on knowledge of the above previously published data, we outlined and completed three sets of animal experiments. In the first series of experiments an attempt was made to duplicate the work of Blakemore and Lord, and of Hufnagel, in quick-freezing the grafts and storing them at about −70 degrees centigrade. The second series was to investigate further the feasibility of preservation and use of heterografts (from one species to another). The third series was designed to investigate the preservation and use of homografts (from an animal of the same species); storing the grafts at temperatures just above freezing in appropriate media, the constituents of which were based on formulas developed by others interested in the field of tissue culture techniques and which were suggested to us by J. H. Hanks (17) of the Department of Bacteriology of the Harvard Medical School. We thought that it would be of interest to determine whether various methods of preservation would allow the tissues of a vessel to remain alive; hence, it was decided to parallel our animal experimentations with tissue culture studies of specimens of the preserved vessels (29). Microscopic studies of implanted grafts were also planned; these were conducted (and will be reported) by Alan R. Moritz.

EXPERIMENTAL GRAFTS IN ANIMALS

Grafting into the abdominal aortas of dogs was selected as the method for the operative work. In such a large vessel, anastomoses are easily performed, and it is possible to evaluate the grafts without being hampered by thromboses which are apt to be troublesome when working with small vessels. The arteries to be preserved and tested were taken under sterile conditions from animals which had been sacrificed. The aorta was removed and its

branches were tied with fine silk. It was cut into 3.0 centimeter lengths.

When a segment of aorta was to be implanted into a recipient animal the technique used was as follows: The dog was anesthetized with intravenous nembutal and the abdomen was opened through a left rectus incision. The abdominal aorta, between the renal arteries and the inferior mesenteric artery, was exposed and freed of branches for a distance of about 5.0 centimeters. It was then occluded in two places, either by the use of aortic clamps such as described by Gross and Hufnagel (12), or by the use of tape tourniquets, and severed between the two occluded points. A generous cuff was left beyond each clamp or tourniquet. After an aorta was thus divided, its cut ends retracted for a distance of approximately 3.0 centimeters; the graft to be tested was sutured into place between those ends (Fig. 4). The anastomoses were made by a single, continuous everting mattress stitch, using 5–0 Deknatel silk on an atraumatic needle. The insertion of such a graft took an average of 45 minutes, following which the clamps or tourniquets were removed. The peritoneum was then brought together over the aorta and the abdomen was closed. No chemotherapy or anticoagulants were used. No damage to the spinal cord or hind limbs was observed as a result of the occlusion of the aorta during these operations.

Series A: implantation of aortic homografts (preserved at −70 degrees centigrade). Twelve grafts were carried out with vessels which had been preserved at −70 degrees centigrade. The segments of aorta were obtained from donor dogs and placed in sterile test tubes which were hermetically sealed. Seven of these contained room air. In the five remaining tubes, the air in the tube was replaced by an atmosphere of helium under pressure of 20 to 40 millimeters of mercury above atmospheric level. This was done in an attempt to repeat the work of Hufnagel (20) who felt that helium (particularly under pressure) was a better conductor of heat than was air and hence would allow quicker freezing of the vessel.

When sealed, the test tube containing an aortic segment was immersed in a beaker containing 300 cubic centimeters of 95 per cent alcohol in which was floating one-half its volume of carbon-dioxide ice. The temperature of this mixture was −72 degrees centigrade. The tubes were kept in this for 15 minutes, and were then stored in a carbon-dioxide ice refrigerator at a temperature of about −70 degrees centigrade. The vessels were stored in this manner for lengths of time varying between 2 and 35 days. When a vessel was to be implanted into a recipient dog, it was thawed by immersing its test tube for 10 minutes in a bath of water at 35 degrees centigrade, after which it was removed from the tube and placed in a bowl of Ringer's solution at the operating table. It was then sutured into the abdominal aorta of a recipient dog, as described previously. Table I shows the results.

Fig. 1. Blood vessel in Ehrlenmeyer flask containing nutrient medium, ready for storage in refrigerator.

It will be seen that of 12 dogs, 1 dog died of pneumonia in 19 days, 2 dogs survived for at least 6 months with fairly good arterial pathways, and 9 died of breakdown of one of the anastomoses. The grafts which broke down did so between 2 and 12 days in 7 cases, and at 20 and 30 days in the other 2. Examination of these 9 autopsy specimens showed that the grafts themselves were friable and necrotic to the point of allowing the sutures to pull out

TABLE II.—RESULTS OF IMPLANTATION OF HETEROGRAFTS (PRESERVED IN 10 PER CENT DOG SERUM IN BALANCED SALT SOLUTION AT 1 TO 4 DEGREES C.) INTO DOG AORTAS

Recipient dog No.	Source of graft	Length of time vessel preserved	Length of life of dog post-operatively	Cause of death	Fate of graft
198–47	Hog	5 hours	5 months	(Still alive)	Aneurysmal dilatation of graft by aortogram
204–47	Hog	7 days	90 days	Sacrificed	Completely thrombosed
209–47	Hog	14 days	4½ months	Sacrificed	Excellent
215–47	Hog	21 days	30 days	Pneumonia	Excellent
223–47	Baboon	4 days	4 months	Sacrificed	Marked intimal sclerosis
230–47	Baboon	12 days	22 days	Hemorrhage	Disintegrated
6–48	Baboon	33 days	3½ months	(Still alive)	Completely thrombosed as shown by aortogram
49–48	Human	38 days	2 months	(Still alive)	Great dilatation of graft as shown by aortogram

before fibrous union had taken place. In our hands, this method of preservation by freezing gave highly unsatisfactory results.

Series B: implantation of aortic heterografts (preserved in balanced salt solution and 10 per cent dog serum at 1 to 4 degrees centigrade). A small number of heterografts were transplanted into dogs, to study the effects of transfer of arteries from one species to another. Four vessels from a hog, 3 from a baboon, and 1 vessel from a human were grafted into abdominal aortas of dogs. These vessels were obtained within 2 to 3 hours of death and were stored, at from 1 to 4 degrees centigrade, in a balanced salt solution to which 10 per cent dog serum was added. (The method of preservation is fully described in Series C.) The vessels were stored for varying periods of time before being implanted into recipient animals, as recorded in Table II.

Examination of Table II shows that the use of baboon aorta was uniformly unsatisfactory, while 3 of the hog vessels and the one piece of human vessel were partially successful in carrying blood for protracted periods of time. This small series of experiments in transplanting vessels from one species to another would seem to indicate that success or failure will depend upon the immunological reaction between the two species involved in the transfer. In some combinations, heterografts seem to live, whereas, other combinations of heterografts cause an intense reaction which leads to rapid degeneration or thrombosis of the implanted vessels.

Series C: implantation of aortic homografts (preserved in balanced salt solution and 10 per cent dog serum at 1 to 4 degrees centigrade). Twenty-five experiments were carried out with segments of aorta which had been stored in a medium which would supply minerals and nutrient elements to keep the tissue of the vessel alive. Each segment was obtained in a sterile manner and was then placed in a sterile 25 or 50 cubic centimeter Ehrlenmeyer flask which contained enough of the nutrient medium to just cover the graft. The medium was composed of 10 per cent homologous (dog) serum in "balanced salt solution"[1] which was maintained at a fairly constant *p*H by means of a buffer. To this medium was added enough of the salts of penicillin and streptomycin to give a concentration of 50 units of each drug per cubic centimeter of fluid. The flask was closed with a sterile cotton stopper and placed in an electric refrigerator of the hospital's blood bank, which is maintained with great care between the temperatures of 1 and 4 degrees centigrade. (A cotton stopper was used originally to allow free diffusion of carbon dioxide and oxygen, but subsequent studies show that a rubber cap is equally satisfactory and is probably more efficient in maintaining a suitable *p*H range in the flask contents.) After

[1]The balanced salt solution is a modification of Tyrode's solution prepared and supplied to us by J. H. Hanks. It is made as follows:

Stock solution, contents per 250 c.c.: NaCl 20 gm.; KCl, 1 gm.; $MgSO_4 .7H_2O$, 0.2 gm.; $MgCl_2 .6H_2O$, 0.2 gm.; $CaCl_2$, 0.35 gm. (dissolved separately); Na_2HPO_4, 0.15 gm. (0.38 gm. of $Na_2HPO .12H_2O$); $KHPO_4$, 0.15 gm.: glucose 2.5 gms.; 0.4 per cent phenol red, 12.5 c.c.

Buffer: 1.4 per cent $NaHCO_3$.

The stock solution is stored at room temperature with 1 c.c. chloroform.

The final solution is made by diluting the stock 1:10, autoclaving, and adding 0.5 c.c. buffer (previously autoclaved) per 20 c.c. This is stored in cotton-stoppered containers in the icebox; it has an equilibrium at about *p*H 7.6

preservation in this manner, and before grafting, a segment of vessel has physical qualities very similar to those of a fresh vessel. This is in contrast to the frozen vessels of Series A, which were often quite friable when thawed out.

We do not mean to imply that the temperature range of 1 to 4 degrees centigrade is necessarily the most optimum one for storage of blood vessels. Indeed we have not extensively studied the preservation of tissue at many ranges of temperature above freezing because there seems to be little practical value in pursuing such investigations. We believed it to be worth while to study methods of preservation only at the low temperatures of refrigeration which are available to us and to many surgeons, such as that commonly used in blood bank storage systems where the range is usually 1 to 4 degrees centigrade.

As we have used it, this method has proved extremely satisfactory. It will be seen that among the 25 dogs with implanted grafts we had no deaths from disruption of the graft. There were 3 instances of complete thrombosis. In 1 of these, a vessel which had been preserved for 1 day, the graft was larger in diameter than the recipient aorta when implanted, giving an effect like that of a slight aneurysm. In the 2 others the grafts had been preserved for 56 days and 98 days respectively, which is considerably longer than we can now recommend for reliable preservation of grafts. In the remaining 22 dogs the grafts were known to be carrying blood at intervals from 4 days to 10 months after operation (Table III).

When viewed grossly at postmortem examination, the vessels were quite satisfactory save for the 3 which were wholly thrombosed. There was very little reaction in the retroperitoneal tissues around the grafts. Inspection of the intima of the grafts in the sacrificed animals has shown 4 which had small, insignificant, mural thrombi. One animal, which died of hepatitis 20 days after implantation of a 34 day preserved graft, showed a thickened, irregular suture line. One graft, sacrificed 3 months after implantation of a 5 day preserved specimen, showed considerable intimal sclerosis. All of the remaining grafts which have been examined after sacrifice have been in excellent condition by gross examination (Fig. 6). A few of the grafts seemed to be thinned somewhat. In several specimens the grafted portion of aorta was much less elastic than were the neighboring portions of host aorta.

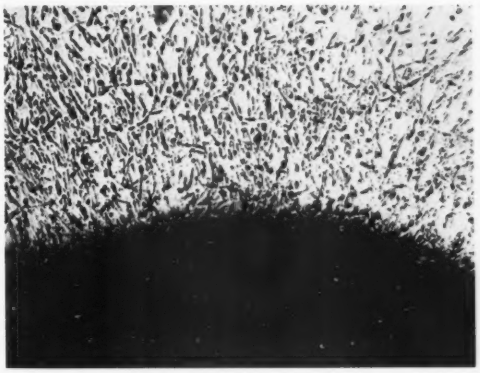

Fig. 2. Photomicrograph of tissue culture of piece of dog aorta after 28 days of storage in 10 per cent homologous serum in balanced salt solution. The black mass in the lower third of the picture is the border of the original piece of aorta. The lacy substances in the upper two-thirds of the photograph are viable and growing cells, indicating that the specimen of aorta is alive after the 28 days of storage.

Eight of the 25 dogs have not yet been sacrificed. Their grafts will be examined after

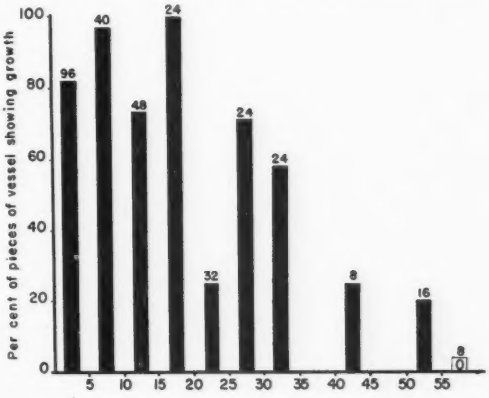

Fig. 3. Results of tissue culture studies to test viability of pieces of dog blood vessels which had been stored in 10 per cent homologous serum in balanced salt solution at 1 to 4 degrees C. The number above each column indicates the number of tissue culture tests which were made. Most of the vessels appeared to be viable for 35 to 40 days.

TABLE III.—RESULTS OF IMPLANTATION OF HOMOGRAFTS (PRESERVED IN 10 PER CENT DOG SERUM IN BALANCED SALT SOLUTION AT 1 TO 4 DEGREES C.) INTO DOG AORTAS

Recipient dog No.	Length of time vessel preserved	Length of life of dog after operation	Cause of death	Fate of graft
157–47	1 day	43 days	Sacrificed	Thrombosed. (Graft larger than host aorta when implanted)
149–47	2 days	3 months	Sacrificed	Good. Small mural thrombus
156–47	2 days	45 days	Sacrificed	Good. Small mural thrombus
30–48	2 days	5 months	(Still alive)	Excellent by aortogram
142–47	3 days	3 months	Sacrificed	Good. Tubular mural thrombus
159–47	4 days	3 months	Sacrificed	Excellent
143–47	5 days	3 months	Sacrificed	Good. Considerable intimal sclerosis
144–47	6 days	6 months	Sacrificed	Good. Slight dilatation
151–47	6 days	6 months	Sacrificed	Excellent
162–47	7 days	15 days	Sacrificed	Excellent
183–47	7 days	6 months	Sacrificed	Excellent
148–47	10 days	10 months	(Still alive)	Excellent by aortogram. ? Small mural thrombus
153–47	10 days	10 months	(Still alive)	Excellent by aortogram
187–47	14 days	12 days	Sacrificed	Excellent
191–47	19 days	8 months	(Still alive)	Excellent by aortogram. ? Tiny mural thrombus
170–47	20 days	6 months	Sacrificed	Excellent
178–47	28 days	11 days	Pneumonia	Excellent
61–48	30 days	5 months	(Still alive)	Excellent by aortogram. ? Tiny mural thrombus at the suture line
25–48	34 days	20 days	Hepatitis	Fair. Small mural thrombi Graft poor color
80–48	40 days	3 months	(Still alive)	Excellent by aortogram
44–48	42 days	5 months	(Still alive)	Excellent by aortogram
55–48	56 days	35 days	Sacrificed	Completely thrombosed
67–48	70 days	4 months	(Still alive)	Excellent by aortogram
79–48	84 days	4 days	Intussusception	Excellent
78–48	98 days	20 days	Sacrificed	Completely thrombosed

longer periods of time. In each of these 8 animals the graft has been studied during life by means of aortography, employing roentgen visualization of the abdominal aorta (Fig. 5). In all of these 8 dogs the aortic graft is patent and has the same caliber as the adjacent host aorta. In 3 of them there are one or several tiny irregularities at anastomotic lines, which probably are insignificant mural thrombi, and which do not diminish the caliber of vessel lumina to any important degree.

Inspection of Table III will show that storage of the grafts for more than 50 days appears to be unsatisfactory. Of the 4 vessels kept for more than 50 days before grafting, 1 was not available for study because the animal died on the fourth day from intestinal obstruction, 2 vessels were thrombosed, and only 1 was wholly satisfactory. Of the 21 grafts stored less than 50 days before implantation, 20 were satisfactory and only 1 was unsatisfactory. It is noteworthy that in this whole series not one animal died from breakdown of a graft.

TISSUE CULTURE EVALUATION OF METHODS OF ARTERIAL PRESERVATION

The vessels which were used in all three experimental series were examined by making tissue cultures of them at appropriate intervals to determine their viability (Fig. 2). These tissue cultures were made under the guidance of J. H. Hanks and John Enders. The work will be described in greater detail elsewhere (29), but the principal results are summarized herewith.

In the first part of this work 8 pieces of tissue were cultured from each of 12 dog aortas, the pieces of vessel being obtained within 2 to 5 hours after death of the animals. Of the 96 pieces of vessels which were so planted, 91 grew out fibroblastic cells.

Study of portions of dog aorta which had been stored at −70 degrees centigrade (Series A) showed that planting of 34 such specimens led to growth in only 2 instances. The freezing and thawing process doubtless had killed the tissue cells in most instances.

Studies of baboon aortas, hog aortas, and human aortas, each of which had been stored in the cold in balanced salt solution containing 10 per cent dog serum (Series B), showed that most of the vessels were living after more than a month.

Detailed studies were made of dog aortas, each of which had been stored at 1 to 4 degrees centigrade in balanced salt solution containing 10 per cent dog serum (Series C). Samples of the vessels were planted at varying times after initial storage of them, to determine how long the vessels were in a viable state. Figure 3 summarizes the data which were obtained. It will be seen that most of the vessels were living and could be grown out on tissue culture for as long as a month or more. After 30 or 35 days there was a marked diminution in the number of aortas which were still living. After 55 days all vessels were found to be dead. These studies lead us to believe that arteries can be stored and kept viable for a little more than a month by the technique which is described in detail under Series C.

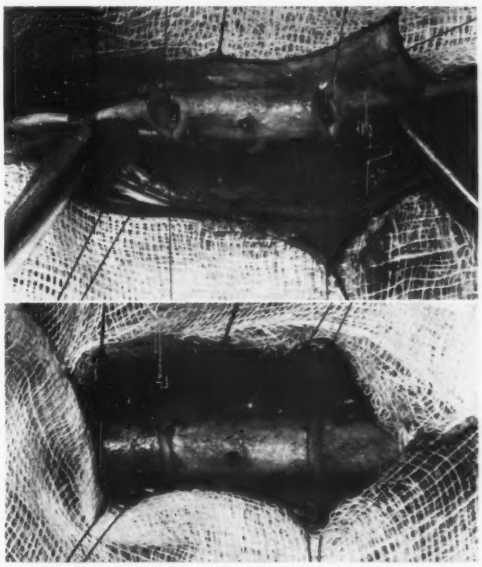

Fig. 4. Preserved aortic graft being implanted into abdominal aorta of a dog. a, above, Graft in place. b, Completion of anastomoses (everting, continuous, mattress suture employed).

DISCUSSION

We believe that there are three main factors which might influence the success or failure of an arterial graft: (1) the viability of the vessel at the time of implantation; (2) the degree of the immunological reaction between the host and the graft; and (3) the technique employed in making the anastomoses.

In our work with dogs, we have had good results with the transplantation of arterial homografts which had been stored at low temperature in 10 per cent homologous serum in balanced salt solution. We have set certain time limits for obtaining the blood vessel segments after death of the donor; a period of 3 or 4 hours is satisfactory, but it probably should not exceed 6 hours. Vessels removed as long as 6 hours after death were found to be still viable by tissue culture studies, and successful transplants could be carried out with them. Beyond 6 hours we felt that there was a likelihood of rapid appearance of postmortem change and of bacterial contamination.

From animal experimentation we found that vessels could be stored (at low temperature and in 10 per cent homologous serum in balanced salt solution) and subsequently used for grafting into other animals of the same species. The upper limits of safety for storing vessels under these conditions is probably in the region of 35 or 40 days. We have selected this limit because aortic grafts in dogs were successful up until this time, and thereafter began to fail. Furthermore, tissue culture studies also indicated that viability of vascular segments is maintained for approximately 35 or 40 days and then rapidly declines.

If we include the preliminary series of fresh homografts transplanted into dog aortas, re-

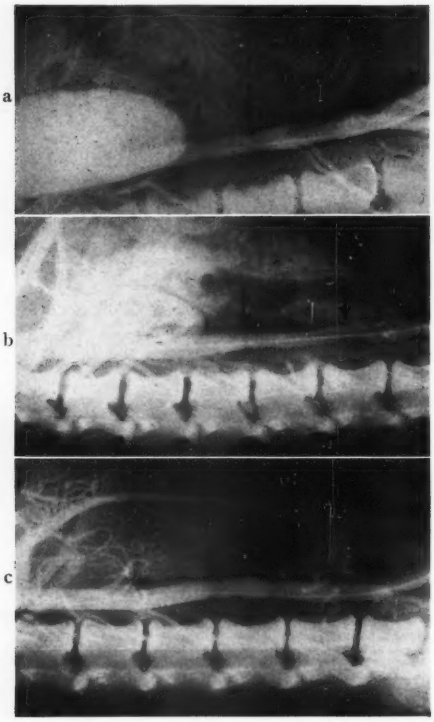

Fig. 5. Aortograms of homografts in abdominal aortas of dogs, made during life by diodrast injection through a catheter which had been threaded up from the femoral artery. All of the grafts had been previously stored in 10 per cent dog serum in balanced salt solution at 1 to 4 degrees C. The graft is the segment between the two arrows. In each instance the graft is patent. a, Dog 170-47. Graft stored for 20 days. Aortogram made 6 months after insertion of graft. b, Dog 44-48. Graft stored for 42 days. Aortogram made 2 months after insertion of graft. c, Dog 67-48. Graft stored for 70 days. Aortogram made 1 month after insertion of graft.

ported by Gross and Hurwitt (12), we have now observed in this laboratory the results of four categories of aortic grafts. They are: (1) fresh homografts; (2) homografts from tissue preserved by quick freezing to about −70 degrees centigrade; (3) heterografts (hog to dog, baboon to dog, and human to dog) from tissue preserved in 10 per cent dog serum in balanced salt solution; and (4) homografts from tissue preserved in 10 per cent dog serum in balanced salt solution. In our hands, the three series in which the grafts could be shown to be viable up to the time of implantation were much more successful than the series of homografts preserved by quick freezing, in which life could seldom be demonstrated by tissue culture. It is important to note that the homoplastic tissue preserved in a living state (up to 42 days) in the balanced salt and 10 per cent serum mixture was as satisfactory as fresh tissue for grafting. From our various observations we believe that a graft is more apt to be successful if it is viable[1] when implanted.

The factor of immunological reaction between graft and host is exceedingly difficult to evaluate. Our series of heterografts is small, and no conclusions can be drawn therefrom. However, it was a distinct surprise to find that any of the grafts from one species to another would survive. Indeed, the microscopic structure of the grafts which were transferred from hog to dog showed better preservation of the media than was the case in any of the dog to dog homografts. The grafts from baboon to dog, on the other hand, were very poor, both grossly and microscopically. This raises the interesting possibility that the transplantation of heterografts between certain species may be practical. If it could be proved, for example, that vessels of sheep, dog, or hog could be used successfully in human beings, we could have available a relatively convenient source of blood vessel grafts. The successful transplantation of fresh dog arteries to the femoral artery in 3 human beings is being reported by Oudot (26), from Paris. He stated in a personal communication (27) that dog vessels were used rather than human arteries because French law prohibits autopsy (and any chance of procuring vessels from a dead body) until 24 hours postmortem. He was able to demonstrate, by arteriography, that the dog vessel grafts were patent, but he did not state how long after operation these roentgenographic studies were made.

While our laboratory experiences convinced us of the dependability of homografts—as far as dog to dog is concerned—there is, of course,

[1]We have had some measure of success with a small series of 15 grafts which were definitely known to be nonviable. These grafts were stored in 4 per cent neutral formalin for from 10 to 25 days, were then rinsed thoroughly in buffered salt solution, and implanted into recipient animals. All grafts carried blood well for several months, but roentgenograms of some of these show calcification in the graft walls.

considerable doubt regarding the possibility of safely transferring arteries from one human to another. While it is true that there might be no correlation between what occurred in dogs and what might happen to homografts in humans, our laboratory experiences did give us some courage to attempt grafts in patients for bridging gaps in large arteries or in the aorta when the circumstances at the operating table demanded such therapy.

ARTERIAL GRAFTS IN HUMAN CASES

Segments of large arteries, or aorta, have been accumulated from human subjects who have died in automobile accidents and from whom we were able to get the material by the courtesy and co-operation of the medical examiner. In all instances the vessels were removed within a few hours after death of the individual, and in no instance was the time lapse greater than 5 hours. The body was always opened under aseptic conditions (operator with cap, mask, sterile gown, and gloves; skin preparation with tincture of iodine; sterile drapes, instruments, etc.). The acquired segments of vessel—iliac, carotid, subclavian, and aortic—were preserved in individual flasks and just covered with the balanced salt solution described previously under Series C, except that the 10 per cent serum was human in origin. These flasks were then stored in a carefully regulated refrigerator (of the hospital's blood bank) at 1 to 4 degrees centigrade.

Eight of these human grafts have been implanted into patients who had a cyanotic type of congenital heart disease, and in whom it was desirable to make some sort of a shunt of blood (the Blalock-Taussig principle) from the aorta or one of its branches into the pulmonary artery. Ordinarily it is possible to bring such vessels together for a direct anastomosis by the Blalock (2) or the Potts (30) techniques, but under some circumstances it is very difficult to establish such shunts without excessive tension on the suture lines. While we hasten to express the opinion that direct anastomoses will in the majority of cases prove to be superior to any method which employs an interposed vessel, it is also probably true that the use of a graft in an occasional case (which will allow arterial junctions to be made without the slightest tension) will give a result which is better than that which would have been obtained from a poor, direct anastomosis. These same general principles also will probably hold true for treatment of coarctation of the aorta. Excision of a constricted segment and anastomosis of the remaining ends of aorta give a very satisfactory result in most cases, but in some instances a very long portion of aorta must be excised, or else the remaining aortic ends are inelastic and cannot be easily apposed. Under either set of circumstances the use of an interposed graft may prove to be the most satisfactory method of re-establishing an aortic pathway of normal size. The validity of this statement is suggested by the pleasing result obtained in Case 9, wherein a graft was

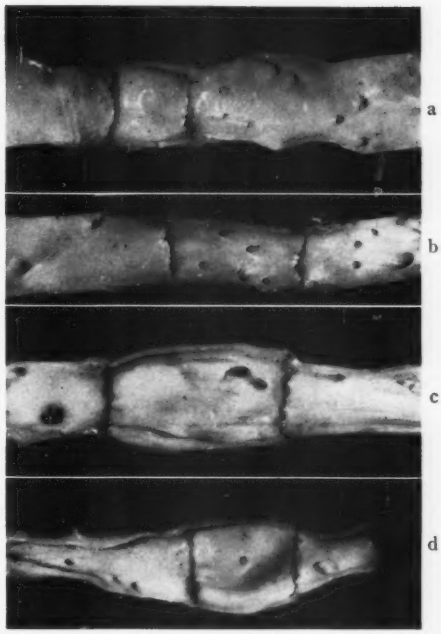

Fig. 6. Photographs of homografts in abdominal aortas of dogs. Prior to their implantation, all grafts had been preserved in 10 per cent dog serum in balanced salt solution at 1 to 4 degrees C. a, Dog 159-47. Graft stored 4 days; animal sacrificed 3 months after implantation. b, Dog 187-47. Graft stored 14 days; animal sacrificed 12 days after implantation. c, Dog 183-47. Graft stored 7 days; animal sacrificed 6 months after implantation. d, Dog 170-47. Graft stored 20 days; animal sacrificed 6 months after implantation.

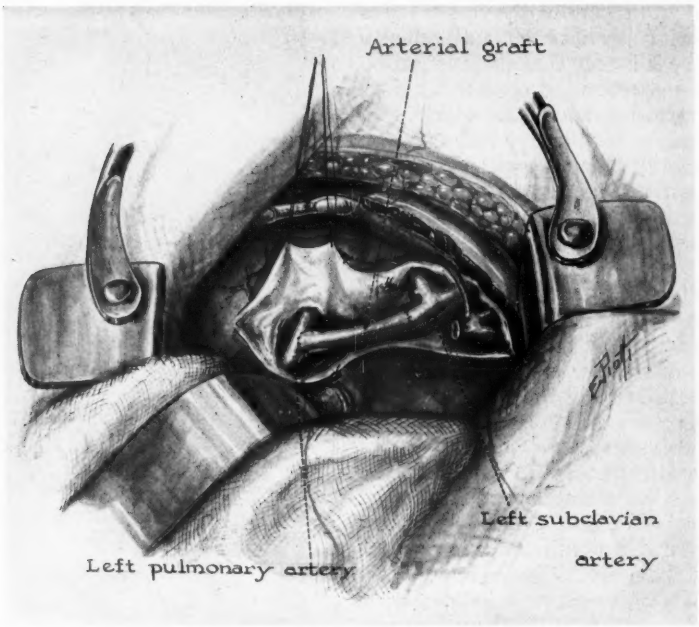

Fig. 7. Treatment of tetralogy of Fallot (Case 2) by insertion of a human arterial graft between the left pulmonary artery and the proximal end of the left subclavian artery. (Patient had a right aortic arch and an innominate artery on the left.) The graft had been secured from another human and had been preserved for 14 days before insertion into the recipient patient.

used to repair an aortic defect after excision of a coarctation. A brief summary of each case follows:

CASE 1. D. E., a 5 year old boy, had been cyanotic since birth and had great limitation of physical activity. On physical examination there was marked cyanosis, clubbing of the fingers and toes, and a harsh systolic murmur in the pulmonic area. Roentgenograms of the chest gave findings typical of a tetralogy of Fallot. Electrocardiograms showed a right axis deviation. The red blood count was 7.6 million. At operation on February 6, 1948, a 3 centimeter segment of (adult) iliac artery, which had been preserved for 2 weeks, was sutured into place between the left pulmonary artery and the proximal end of the left subclavian artery. During the 5 months since operation the child has had great alleviation of his cyanosis and has had a marked increase in his tolerance for exercise. The red blood count has fallen to 5.5 million. There is a continuous murmur in the pulmonary area of the precordium.

CASE 2. W. P., a 4½ year old child, deeply cyanotic since birth, had had a right-sided hemiplegia since the age of 2, this neurological damage being presumably on the basis of thrombosis of intracranial vessels. A faint systolic murmur was audible in the pulmonary area. The red blood count was 9.8 million and the hematocrit was 87 per cent. He had insufficient strength to do more than sit in bed. Roentgenograms and electrocardiograms were typical of a tetralogy of Fallot; the aortic arch was on the right. At operation on February 11, 1948, a human arterial graft, 2.5 centimeters long, which had been preserved for 14 days, was sutured in place between the proximal end of the left subclavian artery and the side of the left pulmonary artery (Fig. 7). During the 5 months that the boy has been followed since operation his general condition has been dramatically improved. The red count has fallen to 5.8 million. He can now walk considerable distances and has a marked alleviation of his cyanosis. A continuous murmur is audible in the left second intercostal space anteriorly.

CASE 3. S. F., a 10½ year old girl, had been cyanotic since birth, and was able to walk only 75 yards at a time. Auscultation revealed a pulmonic systolic murmur of moderate intensity. Roentgenograms, electrocardiograms, and cardiac catheterization all gave findings which were compatible with a tetralogy of Fallot. The aortic arch was on the right. At operation on March 2, 1948 a human arterial

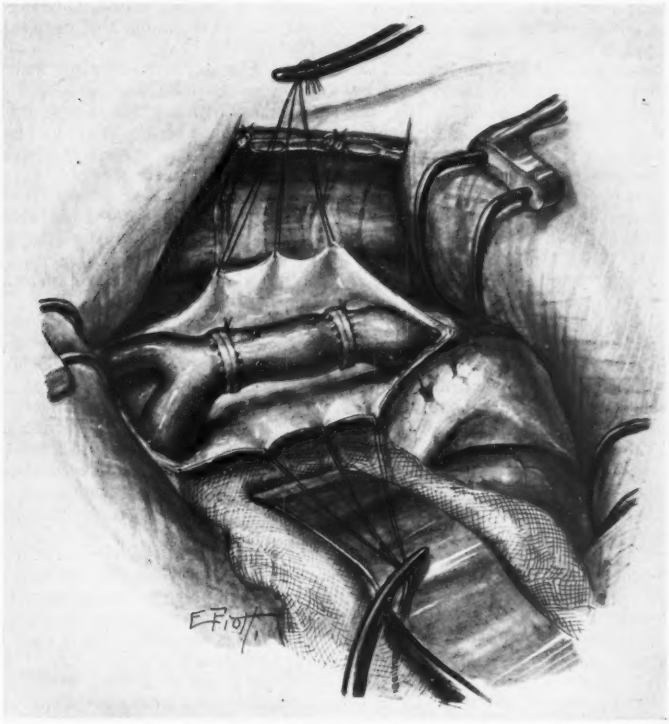

Fig. 8. Treatment of coarctation of the aorta (Case 9) by removal of narrowed segment of aorta and insertion of a human aortic graft. The graft had been procured from a human who had died in an automobile accident; it had been preserved for 28 days in 10 per cent human serum in balanced salt solution at 1 to 4 degrees C. before insertion into the recipient patient. The graft was 5 centimeters in length.

graft, which had been preserved 1 day, was placed between the right subclavian artery and the side of the right pulmonary artery. Dicumarol therapy was given postoperatively; on the tenth day bleeding began from the nose, mouth, gastrointestinal tract, into the right pleural cavity, and manifestations of intracranial neurological disturbances appeared. Because the blood in the right side of the chest could not be satisfactorily aspirated, a thoracotomy was performed on March 16, 1948, to remove clots. The child died the following day, largely from the neurological complications of the anticoagulation therapy. Postmortem examination showed the graft and shunt to be patent and in good condition, without evidence of leakage or thrombosis. The thoracic bleeding had apparently come from the musculature of the chest wall.

CASE 4. L. B., a 12 year old girl, had been cyanotic since the age of 3 to 4 months. She was barely able to climb one flight of stairs. On physical examination there was marked cyanosis, advanced clubbing, and a systolic murmur of considerable intensity in the pulmonic area. Roentgenograms and electrocardiograms were consistent with a tetralogy of Fallot. The red blood count was 8.7 million. At operation on May 1, 1948 a graft, which had been preserved for 4 days, was implanted between the proximal end of the left subclavian artery and the side of the left pulmonary artery. The child's color was greatly improved for about 24 hours but she then developed congestive heart failure, and died on the second postoperative day. A continuous murmur was heard until death occurred. At autopsy the graft was found to be intact and also to be free of thrombosis.

CASE 5. H. B., a 13 year old boy, was first noted to have persistent cyanosis at the age of 6 years. He was forced to squat and rest after short periods of walking. Physical examination showed moderate cyanosis, well marked clubbing of the fingers and toes, and a loud systolic murmur over the pulmonic area. Roentgenograms of the chest and electrocardiograms

were consistent with a diagnosis of tetralogy of Fallot. The red blood count was 6.2 million. At operation on May 3, 1948, a segment of human aorta, 2 centimeters long (from a 5 year old child) which had been preserved 16 days, was sutured into place between the side of the descending aorta and the side of the left pulmonary artery. Postoperatively, a continuous murmur is audible over the pulmonic area. In the 2 months since operation was performed, this boy has progressed extremely well; his color is greatly improved, his physical activity is strikingly increased, and the red blood count has fallen to 5.2 million.

CASE 6. R. D., an 11 year old boy, had been intensely cyanotic since birth. His activity had been so severely limited that he was barely able to ascend one flight of stairs. Physical examination showed marked cyanosis, advanced clubbing of the fingers and toes, and a systolic murmur over the pulmonic area. Roentgenograms, electrocardiograms, and cardiac catheterization were interpreted as indicating that the patient had a stenosis of the tricuspid valve with an associated large interauricular septal defect. The pulmonary blood flow was believed to be insufficient. At operation on May 6, 1948 a segment of human aorta (from a 5 year old child), which had been preserved 19 days, was interposed as a shunt between the side of the descending aorta and the side of left pulmonary artery. Postoperatively, there is a continuous murmur in the pulmonary area. In the 2 months since operation the boy has had an excellent improvement in color and in tolerance for physical activity.

CASE 7. A. H. was a 7 year old boy who had exhibited rather constant cyanosis since birth and had had frequent spells of fainting, without definite evidence of cerebral thrombosis. He had a low tolerance for exercise, and frequently assumed a squatting position. On examination there was marked cyanosis, clubbing, a thrill and a loud systolic murmur in the third left interspace. Electrocardiograms showed a marked right axis deviation, and fluoroscopic findings were not those consistently found with a tetralogy of Fallot. At operation on May 17, 1948, the pressure in the left pulmonary artery—although not actually measured—was obviously much greater than in most cases of tetralogy and it was very doubtful if an aorta-pulmonary artery shunt would be of value. However, it was decided to attempt such an anastomosis. Because the vessels lay in positions which precluded a direct anastomosis, a graft 2 centimeters in length (which had been preserved 20 days) was sutured into the side of the descending aorta, and its opposite end sewed end-to-side into the pulmonary artery. Only a questionable thrill could be felt in the graft when the clamps were removed; the pulmonary artery pressure was so high that probably little, if any, blood flowed through the shunt. Following operation the boy showed no important changes in color or activity; only a systolic murmur could be heard, in the pulmonary area. He was discharged home unimproved. We believe that the failure to produce beneficial changes in this case was due, not to thrombosis of the graft, but to the fact that the child has some sort of a cyanotic state (such as an Eisenmenger complex) which is not benefited by an aorta-pulmonary shunt.

CASE 8. R. A. was a 12 year old boy who had been cyanotic since birth. There had been moderate limitation of activities, "spells of weakness" and frequent "squatting on his haunches." On examination there was moderate cyanosis, a very loud systolic murmur in the pulmonic area, and mild clubbing. The hemoglobin was 25.8 grams and the hematocrit was 71 per cent. The electrocardiogram showed a right-axis shift. Cardiac catheterization and fluoroscopy gave findings indicative of a tetralogy of Fallot. At operation on May 19, 1948 the left subclavian artery was turned downward but in spite of the fact that the left pulmonary artery was divided (and its distal end turned upward), these two ends of vessel could not be brought together for anastomosis. Therefore, a graft 4 centimeters long (which had been preserved 32 days) was inserted end-to-end between the left subclavian artery and the distal end of the left pulmonary artery. Following operation the boy made an excellent recovery; by the time of hospital discharge the hemoglobin had fallen to 16 grams. Since the operation was carried out there has been a loud, continuous murmur in the pulmonary area, the boy's color has greatly improved, and even though the period of postoperative observation is only 7 weeks it is already obvious that his exercise tolerance is increased.

CASE 9. D. S. was a 7 year old boy who entered the hospital for treatment of coarctation of the aorta. Examination showed a pressure in the arms varying on multiple readings from 130 to 150 millimeters of mercury systolic. No femoral pulsations could be felt, and no blood pressure readings could be obtained in the legs. A systolic murmur of moderate intensity was heard in the precordium. By fluoroscopy the heart was slightly enlarged. At operation on May 24, 1948 a coarctation of the aorta was found about 1.5 centimeters below the origin of the left subclavian artery. The narrowed portion was excised and it was found to have a lumen of only 2 millimeters in diameter. The remaining ends of the aorta could be brought together only with great tension; it was therefore decided to insert a graft. This graft was a segment of aorta removed from a human 28 days previously; it measured 5 centimeters in length. The anastomoses to the aorta above and to the aorta below were made with continuous mattress stitches of silk, piercing the entire thickness of the vessel walls and everting the ends of the vessels (Fig. 8). The anastomoses could be made without the slightest tension. The patient had an uninterrupted convalescence. Following operation there was an excellent pulsation in the arteries of the legs. By the end of the second postoperative week the arm pressures had fallen to 108 millimeters of mercury systolic and the leg pressures had risen to 135 millimeters of mercury systolic.

SUMMARY

A method for the preservation of arterial segments is described. This consists in the storage of vessels at temperatures just above freezing and immersed in a mixture of 10 per cent homologous serum in a balanced salt solution to which are added a buffer, a *p*H color indicator, and streptomycin and penicillin. Vessels to be stored in this manner have been removed from donor animals between 1 and 6 hours after death and have been kept for periods of as long as 42 days before they were successfully transplanted into other dogs. Tissue culture studies have shown that viability is maintained for 35 to 40 days in blood vessels stored in this way.

On the basis of these laboratory investigations, segments of arteries or aortas have been secured from humans who have died suddenly and without sepsis. These vessels have been stored in the manner described, and have subsequently been used for human patients when the need arose to bridge gaps in large arteries. Segments of such preserved arteries or aortas have been grafted into 9 human subjects with results which are very promising and which certainly merit further trial and study.

Since completion of this manuscript, 6 more grafts have been inserted into humans. One of these has been used in the treatment of a tetralogy of Fallot and the other 5 were inserted into the aorta after removal of coarctations. These have been in place from 3 to 9 months and all are still patent.

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TESTOSTERONE PROPIONATE IN THE TREATMENT OF ADVANCED CARCINOMA OF THE BREAST

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RADICAL amputation of the breast is the only known method of treatment which offers the prospect of cure for carcinoma of this organ and is followed by excellent results when the operation is well done and the lesion is still limited to the breast. That it fails in many instances, due primarily to the extent of the lesion when the patient is first seen, is a common experience in every surgeon's practice and has led to the employment of certain therapeutic adjuncts to radical amputation, the most frequently used of which is x-ray therapy. Another adjunct of a more controversial nature which has found intermittent favor over the last fifty years is the production of hormonal imbalance. This has been produced by surgical castration, by irradiation of the ovaries, and more recently by the administration of the male sex hormone, testosterone propionate.

There is considerable laboratory evidence to support the theory that both the estrogens and androgens influence the course of mammary cancer. The administration of estrogenic substances frequently has been shown to result in the formation of mammary cancers in both male and female animals, while Nathanson and Andervont reported that administration of the androgen, testosterone propionate, prevented the development of spontaneous breast tumors in cancer bearing strains of mice. Loeser found that the implantation of testosterone propionate pellets in cancer strains of mice reduced the mortality due to spontaneous cancer from 75 per cent in the controls to 40 per cent in the treated animals.

There has been little clinical evidence to prove that the administration of estrogens, in spite of their widespread and often indiscriminate use, ever results in the production of cancer of the human breast or that the administration of androgens to patients who have cancer of the breast results in any permanent benefit.

From the Tumor Clinic and the John C. Oliver Memorial Research Foundation of the St. Margaret Memorial Hospital.

REVIEW OF THE LITERATURE

In 1941 Loeser first reported the use of testosterone propionate in the treatment of cancer of the human breast. He reported 5 cases. Three of these were said to be free of the disease at the time the pellets were implanted and remained well for 4 years. In 2 cases where the disease was present, no regression was noted, although there was systemic improvement and relief from pain.

In 1939 Farrow treated a series of 33 cases with skeletal metastases seen on the breast service at Memorial Hospital in the city of New York. Testosterone propionate was given in doses of from 5 to 25 milligrams for a total of from 6 to 12 injections. Temporary relief from pain with general improvement in the patient was noted in about half the cases. No patient showed clinical or radiographic evidence of control of the disease and all patients were dead at the time of the report made in 1944.

In 1946, Adair and Herrmann reported their studies on the treatment of 11 cases of advanced carcinoma of the breast. Four of these, "one with soft part and three with osseous metastases, manifested remarkable improvement which consisted in regression of the primary lesion and soft part metastases in the one and an increase in calcification in areas of osseous metastases in the other three." Four other cases did not respond to treatment while the remaining cases were still under treatment without clinical evidence of improvement. Each of these patients received from 2000 to 4,100 milligrams over a period of 2 to 3 months. None of the patients had been observed for longer than 3 months.

Boger reported the case of a 27 year old woman who was bedridden with extensive me-

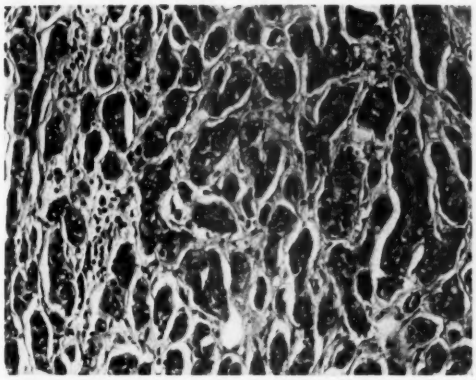

Fig. 1. Case 1. A. McC. Photomicrograph of cutaneous metastasis before testosterone therapy. × 80.

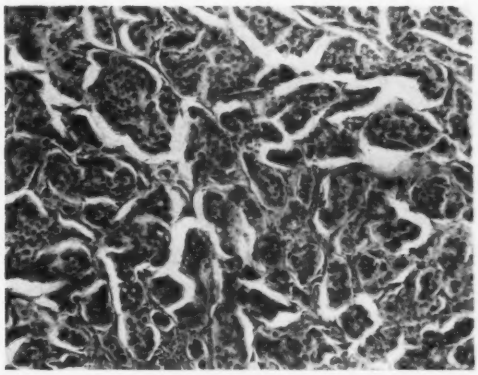

Fig. 2. Case 1. A. McC. Photomicrograph of cutaneous metastasis after 3000 milligrams of testosterone. ×80.

tastases from a cancer of the breast. Surgical castration followed by the administration of 1440 milligrams of methyl testosterone orally resulted in relief from pain and partial recalcification of extensive bone lesions of the spine and pelvis. The relief persisted for 8 months but death occurred 4 months later.

Schwander and Marvin used testosterone in 5 cases with soft tissue metastases in doses up to 1425 milligrams and noted symptomatic relief of pain and an increased sense of well being. Moderate doses had no beneficial effect on the primary lesion or on soft tissue metastases, although the results suggested that recalcification of osteolytic metastases occurred with adequate therapy.

Herrmann, Adair, and Woodard subsequently reported 11 additional cases with osseous metastases. Three of these had received prior irradiation of the lesions without relief from pain. The others were treated solely with testosterone. Symptomatic improvement occurred in 8 patients within 2 weeks after the onset of therapy. The favorable results were obtained with smaller amounts of testosterone than were used in the cases they had previously reported, dosages of 100 milligrams triweekly being found effective.

Fig. 3. Case 3. J. J. Roentgenogram showing metastasis to right humerus with pathological fracture at time of first admission to the hospital.

Fig. 4. Case 3. J. J. Calcification and bony union in pathological fracture following 2400 milligrams of testosterone.

Fig. 5. Case 4. E. S. Roentgenogram showing metastasis to shaft of right radius which appeared after patient had received 3350 milligrams of testosterone.

Herrman and Adair, (8) reported 10 cases with soft tissue metastases. One patient showed marked regression of the primary lesion with disappearance of axillary and supraclavicular metastases after the administration of 3150 milligrams over a period of 2 months. She died of the disease 9 months after the start of treatment. Three others showed cytologic alterations of hydropic changes in cytoplasm and pycnosis of nuclei. There was no gross evidence of regression of the lesions, and all died. The 6 remaining patients showed no response to treatment.

The most optimistic report was that of Prudente from Sao Paulo, Brazil. In 1945 he reported a series of 63 patients with carcinoma of the breast treated since 1939 by radical amputation followed by prolonged prophylactic administration of testosterone propionate in doses of 175 milligrams per week. Comparing them with a series of 64 patients treated prior to 1939 without the use of testosterone, he concluded that there was an improvement in the survival rate among the testosterone treated patients of approximately 100 per cent.

REPORT OF CASES

CASE 1. In the fall of 1946, one of us (J.R.W.) was asked to see a white female, A. McC., aged 50 years, who had cutaneous metastases of the chest wall secondary to a carcinoma of the breast. Five years previously she had had a radical amputation of the left breast performed in another city for a carcinoma. Operation was followed by a course of x-ray therapy and a year later by the intrauterine use of radium to induce an artificial menopause. Four years after her original operation she had had a second course of x-ray therapy for cutaneous metastases, and a year later a rather extensive excision and plastic repair of the involved area which was preceded and followed by a course of Goldblatt's serum. Physical examination 3 months after her last operation revealed a modified left radical mastectomy scar, the presence of several cutaneous metastases over the left anterior and scapular regions of the chest wall, bilateral metastatic invasion of the supraclavicular lymph nodes, and skin changes secondary to radiation therapy. One of the cutaneous metastates had broken down and as a result an indolent ulcer about 2 centimeters in diameter had

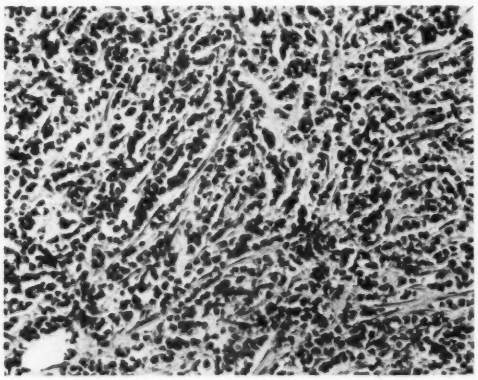

Fig. 6. Case 5. S. D. Photomicrograph of axillary metastasis removed at time of radical operation. × 80.

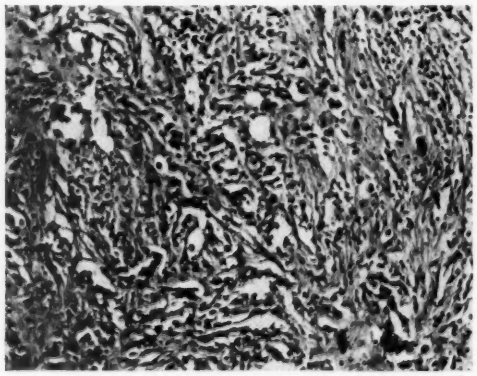

Fig. 7. Case 5. S. D. Metastasis to lymph node of chest wall after 2000 milligrams of testosterone. × 80.

formed. The patient knew the nature of her disease, and both she and her husband were desperate in their search for help.

Testosterone propionate therapy was discussed with them and finally started at their insistence and with their full knowledge as to the uncertainty of the results, as well as to the expense involved. She received 400 milligrams per week for a period of 8 weeks after which the dosage was reduced to 50 milligrams every other week. Two weeks after the institution of therapy she stated that she felt better and thereafter for nearly 3 months the improvement was rapid and sustained. Her appetite improved, she gained weight and strength, and had almost complete relief from pain, not only from the pain of the metastases, but interestingly enough, relief from arthritic pain in her knees and right shoulder which she had had for years. She discarded the cane which she frequently used and changed from an invalid to an energetic woman, even taking a thousand mile auto trip, every minute of which she enjoyed. The skin metastases also appeared to be altered, having taken on a dull cyanotic cast and apparently having diminished somewhat in size, although there was no tendency of the ulcer to heal. The greatest change of all was in her mental attitude for she was convinced that she was going to get well.

Three months after the institution of treatment she began to fail. Histologic sections of cutaneous metastases before and after testosterone therapy showed no change (Figs. 1 and 2). There was a gradual increase in the size as well as number of the cutaneous metastases, some of which broke down to form other ulcers. A tumor, clinically typical of a rapidly growing carcinoma, appeared in the other breast and she died with extensive cutaneous and visceral carcinomatosis 8 months after the start of treatment.

Stimulated by the early changes which occurred in this patient, the problem was submitted to the Tumor Clinic at St. Margaret Memorial Hospital where it was agreed to carry out further investigation on the use of testosterone propionate in the treatment of cases of advanced carcinoma of the breast. This is a report of the above case plus 6 additional cases followed in the Tumor Clinic. The expenses of the investigation were born by the John C. Oliver Research Foundation of the hospital.

In all 7 cases were studied. Four of these were patients who had operable carcinoma of the breast with proved axillary metastases and were treated by radical amputation of the breast and the administration of testosterone. Two had inoperable carcinoma with skeletal metastases, while the seventh case was the one here described, with recurrent carcinoma following prior radical amputation.

Testosterone propionate (perandren) was administered intramuscularly in doses of 200 to 250 milligrams twice a week for a total of 3000 milligrams. It was then reduced to 50 milligrams every other week and continued until the condition of the patient indicated that the disease was progressing in spite of its use, or until the patient died. Exceptions to this were 2 patients in whom treatment was stopped approximately 6 months following radical amputation and who appeared to be well. One patient died early in the course of treatment, having received 1200 milligrams. The 6 other patients received a total amount of the drug which ranged from 3000 to 3900 milligrams. Where possible, cutaneous or lymph node metastases were removed, after the administration of at least 2000 milligrams of testosterone, for microscopic comparison with the original lesions.

CASE 2. E. K., a white female, aged 37 years, was presented to the Tumor Clinic because of a mass in the right breast of unknown duration. Her chief complaint was pain in her "joints" and back which had been present for about 2 years. On physical examination she was found to have a large tumor in the breast, with palpable axillary lymph nodes. There was x-ray evidence of metastases to the lumbar spine, pelvis, and left femur. There was a moderate secondary anemia. An axillary lymph node was removed for microscopic examination and was reported as a metastatic adenocarcinoma, Broders grade four. Testosterone propionate was started in doses of 200 milligrams twice a week. This was followed by an apparent decrease in the size of the remaining axillary lymph nodes, a gain of 4 pounds in weight and sufficient relief from pain to permit her to walk into the out patient department instead of being brought in in a wheel chair. She died 1 month after the start of treatment with the clinical signs and symptoms of a cerebral metastasis. She had received 1200 milligrams of the drug.

CASE 3. J. J., a white female, aged 63 years, was admitted to the hospital as an emergency case with a fracture of the right humerus as a result of a minor trauma. On physical examination she was found to have, in addition to the fracture, a tumor in the left breast which measured approximately 6 centimeters in diameter, together with enlargement of the axillary lymph nodes. She stated that she had known of the presence of the tumor for at least 3 years, but had consulted no one about it because it was not producing any symptoms. X-ray examination of the skeletal system showed osteolytic lesions in the head and neck of the left femur, the left ilium

and the upper portion of the right humerus with a pathological fracture in the latter. Laboratory studies were as follows: red blood cells, 5,120,000; hemoglobin 95 per cent; blood calcium 10.2 milligrams; phosphorous 3.0 milligrams; alkaline phosphatase, 4.28 Bodanski units; urine, normal. An axillary lymph node was removed for pathologic examination and was reported as a Broders grade three adenocarcinoma of breast origin. The fracture was immobilized by means of an abduction splint and testosterone propionate was started in doses of 250 milligrams twice a week. Six weeks after the institution of treatment, the patient returned to the hospital for examination. She had discarded the orthopedic appliance and was using her right arm to feed herself and to comb her hair. She stated that she felt better than she had for the last 5 years and that her friends all commented on how well she appeared. X-ray studies revealed evidence of calcification (Figs. 3 and 4) of the bony lesions with union of the fracture of the right humerus. The dosage of testosterone was reduced to 50 milligrams every other week. As the patient lived in a distant town she was not seen again, although periodic reports indicated that the improvement was maintained until 2 weeks before death when she became jaundiced as a result of liver metastases, and lapsed into coma. She had had very little pain even in the terminal phase of the disease. Her death occurred 6 months after the institution of treatment. She had received 3500 milligrams of testosterone.

CASE 4. E. S., a white female, aged 41 years, was seen in the Tumor Clinic because of the presence of a tumor in the left breast which she had had for 14 months, having first noticed it during the second month of a pregnancy. She went through the pregnancy and was delivered of a normal healthy infant at term. The breast tumor had not been noted by her obstetrician nor did she call anyone's attention to it until 7 months after delivery when she became alarmed because of its increase in size. On examination the tumor was found to measure approximately 5 centimeters in diameter. The lymph nodes in the axilla were enlarged. A blood count and urinalysis were normal. Radical amputation of the breast was performed, the pathologist reporting the lesion to be a Broders grade two adenocarcinoma in a lactating breast with involvement of the axillary lymph nodes. Two hundred milligrams of testosterone were given 1 week after operation and this dosage was continued twice a week for a total of 3000 milligrams. It was then reduced to 50 milligrams every other week. Menstruation ceased after the second injection. The patient repeatedly volunteered the information that she felt fine and her sole complaints were that her voice seemed to have deepened a little and that she occasionally had vague pain in the region of the lower dorsal spine. X-ray studies of the chest, ribs, and spine were negative. Three months after the beginning of treatment she complained of pain and swelling (Fig. 5) in the right forearm just below the elbow and x-ray examination of the area revealed a bone metastasis to the shaft of the radius. Because it had appeared while she was still receiving testosterone, x-ray therapy was used with prompt relief from pain and with evidence of recalcification of the lesion. Ten months after operation she was readmitted to the hospital because of failing vision. An x-ray of the skull was negative but there was clinical evidence of a cerebral lesion, probably of metastatic origin. She died 2 months later. She had received testosterone for the entire year, the total dosage being 3900 milligrams.

CASE 5. S. D., a white female, aged 53 years, was sent to the Tumor Clinic because of a tumor of the left breast which had been present for a year. She had passed through the menopause at the age of 52 years. Physical examination revealed an inflammatory carcinoma involving the entire left breast with palpable axillary lymph nodes. There was no other evidence of extension of the disease, either on physical examination or on x-ray examination of the chest. The lesion was considered to be operable. Laboratory studies showed 4,000,000 red blood cells and 78 per cent hemoglobin. Urinalysis was negative. The blood calcium was 7.2 milligrams and the phosphorus 2.88 milligrams. The alkaline phosphatase was recorded as 3.68 Bodanski units. Radical amputation of the breast was performed for a Broders grade four adenocarcinoma with axillary metastases and was followed by the administration of testosterone propionate in dosages of 200 milligrams twice a week.

There was a gain in weight and a sense of well being. A macular rash appeared on her body but lasted for only a week and disappeared without local treatment and without stopping the drug. After the patient had received 2000 milligrams of testosterone, it was noted that there was an enlargement of the left supraclavicular lymph node together with skin metastases on the chest wall (Figs. 6 and 7) one of the latter of which was removed for microscopic examination. Histologic examination of this tissue showed considerable change in the appearance of the tumor, chiefly fibrosis but with some degeneration of essential cells. This change was not considered specific for testosterone therapy. Testosterone therapy was continued until the patient had had a total of 3150 milligrams. She ultimately developed metastases to the liver, associated with severe pain and died 8 months after operation.

CASE 6. A. F., a white female, aged 64 years, was admitted to the hospital because of diabetes mellitus and the presence of a tumor in the right breast. Physical examination was essentially negative save for generalized arteriosclerosis, the presence of a tumor in the breast which measured 3 centimeters in diameter and palpable lymph nodes in the right axilla. There was three plus sugar in the urine and a blood sugar level of 238 milligrams. After adequate control of the diabetes had been obtained, radical amputation of the breast was performed. The pathologist reported the tumor to be a Broders grade three adenocarcinoma with axillary metastases. Testosterone propionate was started in doses of 250

milligrams, given twice a week until the patient had received 3000 milligrams, and then reduced to 50 milligrams every other week. This was carried out under the supervision of her family physician and was finally stopped after a total of 3500 milligrams had been given, and the patient was apparently well. She remained well for 11 months when cutaneous metastases began to appear in large numbers over the chest wall. She refused any further therapy and died 16 months after operation.

CASE 7. E. G., a white female, aged 45 years, had known of the presence of a gradually enlarging tumor in the left breast for 18 months. Highly intelligent in all other respects, she had consulted no one about it because she feared it might be a cancer. Her physical examination was entirely negative save for the breast lesion which measured 3 centimeters in diameter and for the presence of palpable axillary lymph nodes. Laboratory studies, including blood calcium, phosphorus and alkaline phosphatase determinations were all within normal limits. Radical amputation of the breast was carried out, the lesion being reported to be a Broders grade three adenocarcinoma with axillary metastases. This was followed by the administration of 250 milligrams of testosterone propionate twice a week for a total of 3000 milligrams and then 50 milligrams every other week until she had received 3400 milligrams. Menstruation ceased shortly after the beginning of treatment and did not reappear until a month after the last injection. She felt well and had no disturbing reactions except for a slight deepening of her voice, which was somewhat embarrassing to her in her occupation as a store executive. Medication was discontinued 6 months after operation. She is apparently well without evidence of recurrence 18 months after operation.

RESULTS

In this series of cases the administration of testosterone appears to have had no curative and little inhibitory effect on the disease or its course. Six of the 7 patients treated have died of the disease within 16 months of the institution of treatment. Four of the 7 patients had radical mastectomy for operable carcinoma of the breast with axillary metastases. Three of these are now dead and one is living and apparently well. This is too small a group to have any statistical significance, although the result is no better than that obtained by radical amputation alone. In 2 inoperable cases with bone metastases, there was prompt relief from the pain of such lesions, while in 1 of these, union of a pathological fracture occurred within 6 weeks. No permanent effect was noted on soft tissue metastases. In 3 patients there appeared to be a slight decrease in the size of metastatic lesions to the skin or axillary nodes, but this was a best of temporary duration and the observation is subject to question. In one instance this apparent decrease was associated with a change in the color of several skin metastases from flesh color to a dusky red, but they soon faded again and ultimately broke down to form ulcers. Microscopic examination of soft tissue lesions before and after treatment in 2 cases, failed to show any unusual changes in the appearance of the tumor cells which could be attributed to testosterone. Distant metastases to the liver and brain occurred during treatment, while 1 patient developed a rapidly growing carcinoma in the remaining breast.

TABLE I.—SUMMARY OF CASES

Number of cases treated		7
Operable carcinoma with axillary metastases	4	
Inoperable carcinoma	2	
Recurrent carcinoma	1	
		7
Treatment		
Radical amputation—testosterone	4	
Biopsy—testosterone	3	
		7
Results		
Operable cases		
Living and well without recurrence	1	
Died of disease	3	
Inoperable and recurrent cases		
Living	0	
Died of disease	3	
		7

Laboratory tests carried out before and during the course of treatment revealed no significant alterations in blood counts, urinalysis, blood calcium, phosphorus or alkaline phosphatase studies.

All patients noted an improved sense of well being, so marked in several instances that they volunteered the information that they felt better than they had for years and that their friends remarked on how much better they looked. This improvement appeared within 2 to 3 weeks of the institution of treatment, was most pronounced in those patients showing the greatest debility and persisted for a variable period of from 2 to 5 months. There was an increase in body weight, appetite and strength, and a marked improvement in the mental attitude of those

patients who knew the nature and the prognosis of their disease. Those patients who had pain were relieved during treatment, although they all required narcotics during the terminal stages of the disease.

There were no adverse reactions to the use of testosterone. In those patients in the younger age group, menstruation ceased shortly after the institution of treatment. Deepening of the voice occurred but was not marked enough to be annoying or particularly embarrassing. It was not noted in those patients who had passed the menopause. There was no evidence of hirsutism. One patient had a transient acne which persisted for only a short time and disappeared without altering the course of treatment and was accordingly thought not to be due to the testosterone.

DISCUSSION

The results obtained in this series of cases have not been encouraging and do not seem to warrant the enthusiasm found in some of the other reports. All 7 cases were examples of carcinoma of the breast with metastases. Three were in an advanced stage of the disease when treatment was begun, while the remaining 4 had operable tumors with axillary metastases. In 3 of the operable cases the patients possessed complicating factors such as pregnancy, diabetes mellitus, or an inflammatory type of tumor, all of which are known to give an unfavorable prognosis in this disease. The only operable case in which one of these complicating factors did not exist was Case 7. This is the only patient who is still living. Were testosterone propionate effective in the treatment of carcinoma of the breast, some improvement in results should have been apparent regardless of the stage of the disease. This was not the case in spite of the fact that large doses were given and that 5 of the 6 patients who died were still receiving the drug at the time of death. Not only was the ultimate outcome unaffected but microscopic examination of metastatic lesions removed from 2 patients after the administration of 2000 and 3000 milligrams, respectively, failed to reveal any alteration in tumor cytology which could be attributed to testosterone.

Three beneficial effects were noted; there was a gain in weight and strength with a sense of well-being, there was a decrease in pain, and there was evidence of calcification of bony metastases. All of these were of temporary duration. It is our impression that they were all due to the action of testosterone propionate on the metabolic processes of the body rather than to any specific effect on tumor cells. There is evidence to support this impression.

Kenyon states that testosterone has an anabolic effect on the body, causing a decrease in the urinary excretion of nitrogen, inorganic phosphorus and sulfate, potassium, sodium and creatine, and that its administration results in an increase in the basal metabolic rate and gain in body weight. He found that 25 milligrams daily is an effective dose if the patient is maintained on a constant diet. Butler and his associates found that a reduction in urinary nitrogen occurred even in the presence of a starvation diet with inadequate caloric intake, although a positive nitrogen balance could not be obtained unless the patient was on a diet adequate in calories and protein. Abbott, studying a series of burn cases and noting the effects of diet and testosterone on recovery, stated that patients receiving testosterone and an adequate caloric intake did better than those without testosterone or those on an inadequate diet with or without testosterone. He further stated that a reduction in the amount of urinary nitrogen and a gain in body weight occurs following its administration to normal subjects of both sexes and referred to similar observations having been made on patients with carcinoma of the stomach, hyperthyroidism, Cushing's disease, Simmond's disease, pernicious anemia, hypogonadism, and nephrosis. The amount of nitrogen excreted in the urine could be reduced effectively by giving 12.6 milligrams daily.

Interest has been shown in the effect of hormones on the healing processes of bone. According to Albright, the healing of a fracture is a special form of bone metabolism which is dependent on the formation of an organic matrix through the activity of the osteoblasts. He found that this activity could

be accelerated by three types of stimuli: stresses and strains, diet, and hormones and other chemical and enzymatic substances, that both estrin and testosterone are effective stimulants and that their administration resulted in an increased rate of bone repair. Gardner and his associates think that testosterone may find a practical application in the prevention or alleviation of the symptoms of senile osteoporosis and in the acceleration of the rate of healing of fractures.

The recent observations that testosterone may be effective in some instances in the treatment of bone metastases from carcinoma of the breast may possibly be explained by the stimulation of bone repair at the site of the metastases rather than to any specific effect on the tumor. It is not logical to assume that cancer cells would be altered when they reside in bone but not when they occur in soft tissue. The relief from the pain of bone metastases in 2 patients in this series, as well as the rapid union of a pathological fracture in one of these was thus possibly due to the hormonal stimulation of bone repair.

The temporary duration of the bodily changes which occur following the administration of testosterone has been noted by many observers and apparently is due to the interrelationship between the adrenals, pituitary, and ovaries. Farrow states that "any natural or artificial imbalance caused by either the menopause or castration will be followed by compensatory changes in other endocrine organs and a partial replacement by hormones or compounds having a biologic effect similar to that of those which have become deficient" and consequently that "any imbalance due to excesses or deficiencies of sex hormones may be of a temporary nature." Although our clinical observations would tend to indicate a beneficial effect of many weeks' duration, Kenyon states that the drug may lose its effect in as short a period as 10 days. The appearance of a metastatic bone lesion in 1 patient of this series while under testosterone therapy would tend to indicate the inability of the drug to maintain its effect for any prolonged period of time.

It is possible that the systemic improvement noted following the treatment of 7 patients with advanced carcinoma of the breast with testosterone propionate was due, not to any effect on the tumor cells but rather to the anabolic action of the drug on all the body tissues. It is our belief that it has no place in the management of carcinoma of the breast except as a palliative agent.

SUMMARY AND CONCLUSIONS

1. Testosterone propionate in amounts up to 3900 milligrams was used to treat 7 patients with carcinoma of the breast.

2. In 3 patients with inoperable or recurrent carcinoma it failed to alter the course of the disease and all 3 patients are dead.

3. In 4 patients with operable carcinoma with axillary metastases, administration following radical amputation failed to improve the results ordinarily obtained by radical amputation alone. Three of the 4 patients are now dead.

4. There was no evidence of any specific alteration in tumor cytology in 2 patients in whom metastatic lesions were removed after the administration of 2000 and 3000 milligrams of testosterone, respectively.

5. Systemic improvement consisting of a gain in weight and strength occurred in all cases, being most marked in those with the greatest debility. It appeared within 2 to 3 weeks of treatment, but was of temporary duration, usually lasting for about 3 months.

6. The pain of bone metastases was relieved in the 2 patients who had such lesions when treatment was started, while union occurred in the 1 patient with a pathological fracture. One patient developed a painful bone metastasis while under treatment.

7. There is evidence to show that systemic improvement, relief from pain, and calcification of bone metastases are due to the anabolic effect of the drug on the entire body rather than to any specific effect on tumor cells, that similar improvement occurs when the drug is administered in the presence of other diseases, and that it can be explained entirely by the known action of the drug on the normal subject.

8. No evidence was obtained in this series of 7 cases to indicate that testosterone propionate had any specific inhibitory effect on

advanced carcinoma of the breast, that it altered the course of the disease, or that it resulted in any improvement in the survival rates obtained by the more commonly accepted forms of therapy.

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THE STUDY OF PERIPHERAL VASCULAR DISEASE WITH RADIOACTIVE ISOTOPES

Part II

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THE introduction of the use of radioactive isotopes in the study of peripheral vascular disease has made possible the critical evaluation of the circulation in the tissues of the extremities. Although all methods of instrumental investigation have certain inherent weaknesses, they contribute a valuable addition to the clinical evaluation of vascular disorders. Studies on the circulation in the muscles of the extremities in normal individuals and those with vascular diseases have made possible a more objective evaluation of the patient.

In a previous report, Part I (1), two methods for the use of radioactive sodium 24 in the investigation of circulatory physiology of the extremities were compared and discussed. The electronic apparatus used for these studies was described in detail, and the results of one of the study methods were evaluated. This paper is concerned with an evaluation of the results of the second method.

In brief, a sterile solution of radioactive sodium chloride, consisting of 10 microcuries of the radioactive substance in approximately 0.2 cubic centimeter of solution, is injected into the muscle of the extremity to be studied. The radiation effect on the individual from this quantity of radioactive material is negligible, and frequent repeated observations can be made without danger to the patient. The radioactive sodium emits strong gamma rays which are readily detected by electronic equipment placed outside the body.

The presence of the sodium chloride in the muscle is recorded automatically by an electromechanical device built for these studies (3). As the radioactive salt solution is mobilized into the vascular channels and is removed from the part, the decrease in the amount of sodium chloride in the muscle is similarly detected. Since the amount of radioactive salt solution originally injected is small, after its mobilization into vascular system and subsequent dilution, the amount of radioactive salt returning to the extremity is not significant.

The technique of the procedure consists of placing the patient on a tilt table with the extremities elevated at 35 degrees. A detecting unit (Geiger-Mueller tube) is placed posterior to each gastrocnemius muscle. The radioactive sodium chloride is injected into the muscle, and its rate of disappearance is measured for a period of 10 minutes. The patient may then be placed in a horizontal position, and a similar determination of the rate of disappearance made. In certain instances, drugs have been administered or other measures have been carried out which are believed to enhance the circulation, and their influence on the mobilization of the sodium determined. These findings are to be reported later.

Fifty-seven normal individuals have been studied by this method. It has been found that under basal conditions the disappearance of sodium from the muscle in a given individual is constant. If the rate of disappearance of the sodium is plotted on semilogarithmic paper, a linear expression of the rate of disappearance is obtained. For comparison of results, this linear expression can be converted into numerical terms by an equation first employed by Kety (2):

$$K = \frac{\log C_1 - \log C_2}{.4343\,(T_2 - T_1)}$$

C_1 = counting rate at time T_1
C_2 = counting rate at time T_2

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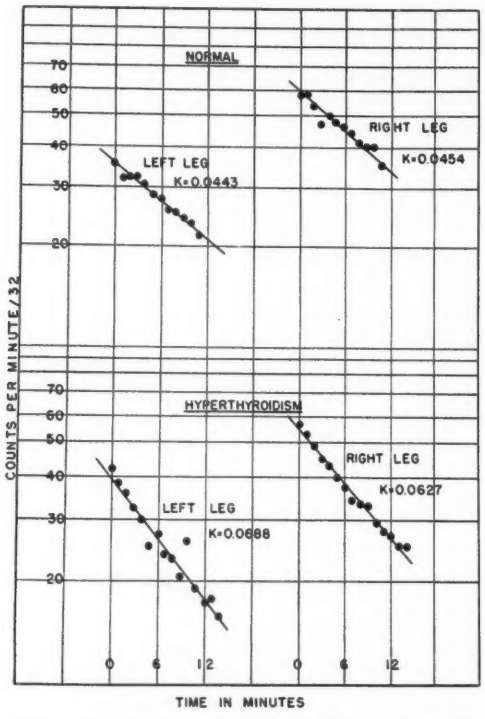

Fig. 1. Graph representing the rate of removal of sodium in a normal person and in a patient with hyperthyroidism.

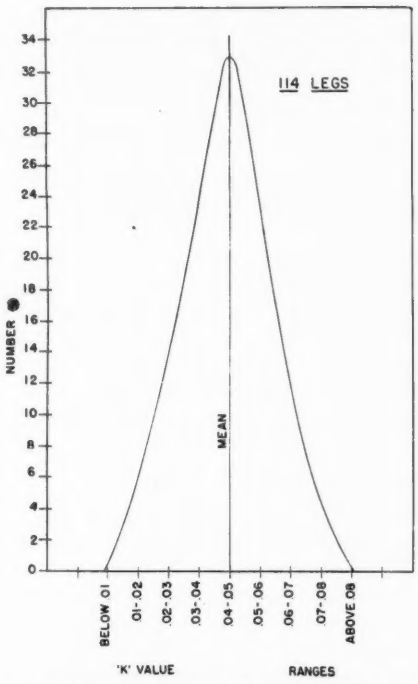

Fig. 2. Distribution curve of the results in the study of 114 normal extremities.

In all individuals, many factors control the rate and volume of blood flow to the extremities, for example, the emotional tone of the patient, excitement or apprehension, the activity of the part, the temperature of the environment, and the presence of edema, infection, or metabolic disturbances. Even though a constantly controlled temperature room is used, and the patient is observed under basal conditions, only a few of the variables can be eliminated.

It has been found that if the individual is unduly apprehensive the mobilization of sodium will be increased above normal during the initial portion of the examination period and will fall below normal after the apprehension subsides. Consequently, it has been found necessary in all individuals to delay the determination of the rate of disappearance for at least 2 or 3 minutes following the injection of the sodium. The patient must be cautioned to remain completely motionless as exercise of the muscle greatly expedites the removal of the sodium, and will thus render the determination inaccurate.

From the observation of 114 normal extremities, a disappearance pattern was obtained which varied only within slight limits (Fig. 1). The factors, previously mentioned, which produce variations in the disappearance rate of the sodium are included. On plotting these determinations as a distribution curve, the pattern becomes statistically significant (Fig. 2).

In individuals of high emotional tone with hypertension, or patients with hyperthyroidism, the mobilization of sodium from the muscle has been found to be uniformly increased. Similarly, if hyperemia of the extremity is produced by application and removal of a tourniquet, the mobilization of the sodium can be initially inhibited and then precipitously and abnormally increased in rate. Follow-

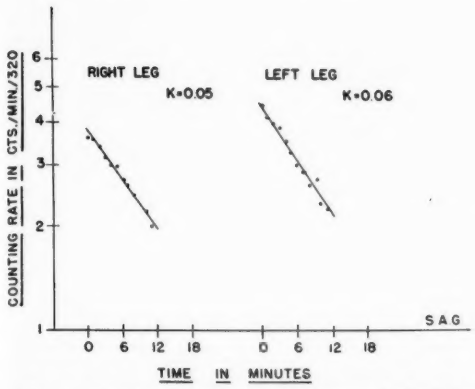

Fig. 3. Graph representing rate of removal of sodium in patient S.A.G. with hypertension; blood pressure of 188/126.

ing the application of a venous tourniquet inflated to diastolic pressure, the removal of the sodium is prevented.

Patients with obliterative arterial disease and with lesser degrees of vasospastic phenomena will repeatedly produce the most constant pattern of sodium removal. In such individuals the variable factors influencing the blood flow in the extremities are apparently minimized. It is believed that in this group particularly, less error would be encountered in the evaluation of specific measures of therapy or operative procedures. Individuals with vascular diseases in which vasospastic phenomena are of more significance demonstrate greater variations during a single period of observation, but they too mobilize sodium at below normal levels, seemingly in proportion to the degree of arterial insufficiency.

One hundred and two patients with various vascular changes have been studied. An effort was made to include patients with all types of circulatory abnormalities. Similar curves were obtained on patients with the same vascular disorder. Representative results obtained in individuals with vascular disturbances are presented here.

Hyperthyroidism. In the 5 patients with hyperthyroidism, the mobilization of the sodium from the extremity was greatly increased (Fig. 1). This might also be expected in patients with increased cardiac output, increased pulse pressure, and peripheral vasodilatation.

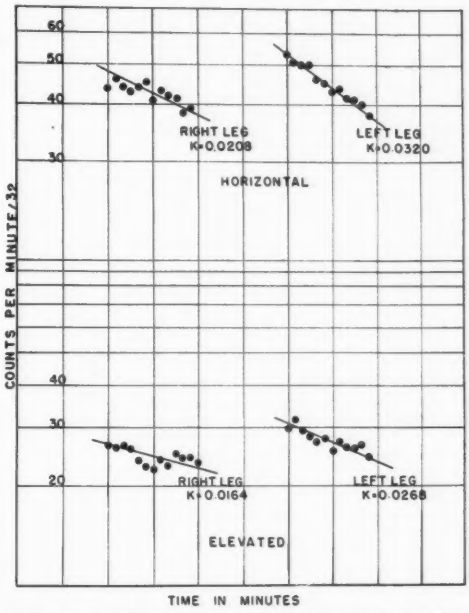

Fig. 4. Graph representing rate of removal of sodium in patient O.D.K. with thrombosis of bifurcation of aorta.

Hypertension. Five patients with essential hypertension without congestive failure were studied. These individuals were of high emotional tone, gave an exaggerated response to the Hines and Brown cold pressor test, and exhibited marked decline in blood pressure upon sedation. They showed an increased rate of removal of the sodium. Sympathectomy and splanchnicectomy were subsequently performed in each case in an attempt to alleviate the hypertension. Following operation there was no significant change in the rate of sodium removal.

S.A.G. (Fig. 3.) Hypertension was discovered in this 30 year old white male during a routine examination for admission to the Air Corps, 8 years previous to this examination. For 18 months previous to admission he noticed increasingly severe headaches.

Physical examination revealed an elevation of blood pressure to 188/126 in both arms. No cardiac or kidney changes were present. Only slight response to the Hines and Brown cold pressor test was noted. Sympathectomy and splanchnicectomy were performed for the hypertension.

Arteriosclerosis obliterans. Twenty patients with varying degrees of arteriosclerotic ob-

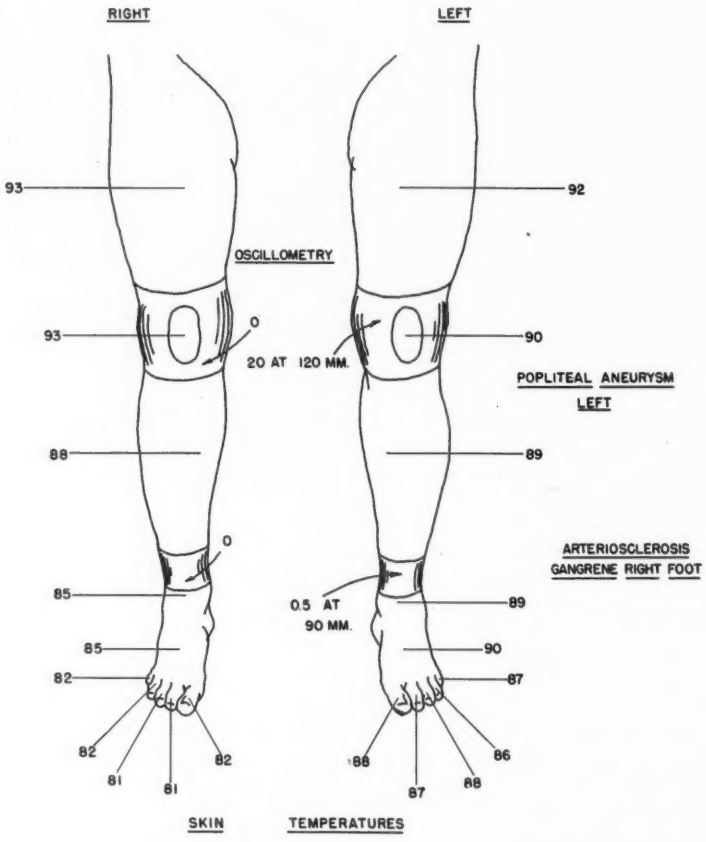

Fig. 5a.

literation of the vascular tree in the lower extremities were studied. It was found that this group of individuals had less variation in the rate of sodium disappearance even in the presence of emotional and psychic factors. However, the degree of elevation of the extremity was found to be important in this group. With moderate degrees of vascular obliteration in which the extremity retained a normal color in the horizontal position, the rate of sodium disappearance was frequently within normal ranges. If the extremity was elevated at an angle of 35 degrees, the rate of the removal of sodium was greatly retarded. With the extremity in this position, the administration of drugs which cause a decrease in blood pressure or generalized vasodilatation resulted in a decrease in rate of mobilization of the sodium.

O.D.K. (Fig. 4), a 49 year old male physician, first noticed an indefinite fatigability of the lower extremities 5 years previous to this examination. Three years ago, following 2 days of strenuous hunting and walking, there was a precipitous increase in the fatigability. Since that time there has been progressive weakness of the extremities, characterized by a feeling of tiredness, aching, and claudication. Occasional numbness of the great toes was noted.

Examination revealed no abnormal color changes in either lower extremity; both became ruborous on dependency following elevation, but no pallor was present on elevation. There was slight trophic change in the skin and nails of the lower extremities. All arterial pulsations were absent in the extremities,

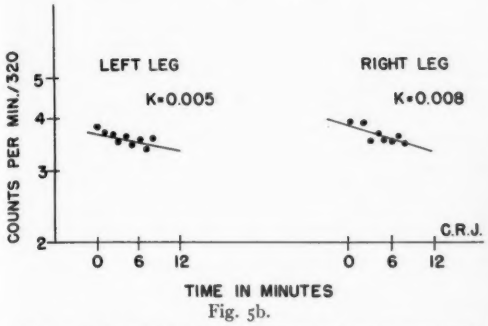

Fig. 5b.

Fig. 5. Patient C.R.J. with arteriosclerosis, popliteal aneurysm and gangrene. a, Graph showing skin temperatures; b, graph representing rate of removal of sodium; c, arteriogram showing obstruction of femoropopliteal junction.

Fig. 5c.

and no pulsation could be felt in the abdominal aorta below the umbilicus. Skin surface temperatures were normal. Oscillometry revealed greatly diminished pulsations at all levels in the lower extremities.

A diagnosis of thrombosis of the abdominal aorta was made.

C.R.J. (Fig. 5a, b, c.) This 86 year old white male stated that he had been active until 3 weeks prior to admission. An accurate history could not be obtained because of his mental confusion. He was awakened at 2 a.m., at the onset of his present condition, with severe pain in the right lower extremity. Shortly thereafter, he noticed that his entire foot was cool, and that a ruborous cyanosis was present.

Examination of the extremities revealed marked pallor of the right lower extremity on elevation. Both lower extremities became ruborous on dependency. There were trophic changes in the skin and its derivatives in both lower extremities. A small gangrenous plaque was present on the lateral aspect of the right foot at the head of the 5th metatarsal. An area of cyanosis was persistent on the dorsolateral aspect of the right foot when in the horizontal position. The dorsalis pedis and posterior tibial pulses were absent bilaterally. The right popliteal pulse was absent. A popliteal aneurysm was present on the left.

Oscillometric examination revealed pulsations to be absent distal from the knee inferiorly on the right, increased in the left knee region over the aneurysm, and diminished at the left ankle. Skin surface temperatures were elevated on the left and normal on the right. An arteriogram (Fig. 5c) was made, revealing an obstruction of the femoropopliteal junction.

A diagnosis of arteriosclerosis obliterans and aneurysm, popliteal, left, was made.

E.H. (Fig. 6), a 76 year old white male, had a history of a cerebral accident 7 years previous to this examination. Since that time he had suffered from claudications in his legs. There was no history of trophic changes in the extremities, nor did physical examination reveal any such changes. Pallor of the feet was present on elevation. Femoral pulses were palpable but oscillometry did not reveal any pulsations from the knees distally. Skin surface temperatures were diminished bilaterally.

A diagnosis of arteriosclerosis obliterans was made.

Thrombophlebitis. Twenty-eight patients with thrombophlebitis were studied. This group was by far the most difficult to evaluate. The sodium was found to mobilize more rapidly with the extremity in the elevated position, if no arterial insufficiency was present. In this position, however, the removal rate of the sodium was usually below normal in the edematous extremity and was always less in the affected extremity than in the opposite or normal extremity. The greater the degree of edema of the calf muscle, the greater was the retention of the salt solution. It was found also that, in general, the higher the skin surface temperature, the greater was the rapidity of removal. In individuals with high skin surface temperatures, the rate of sodium removal was frequently within normal limits.

Even if the extremity had become elephantine in proportion due to an old chronic venous and lymphatic obstruction, with extensive fibrosis in the subcutaneous region, the mobilization of sodium chloride from the muscle was frequently equal to the rate of mobilization in the uninvolved extremity. This was interpreted as indicating that the

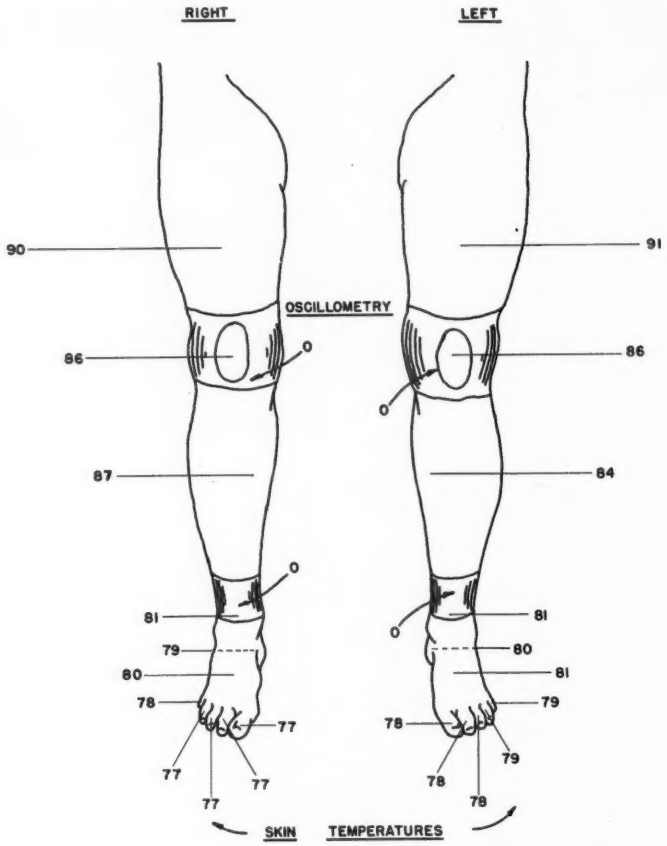

Fig. 6a.

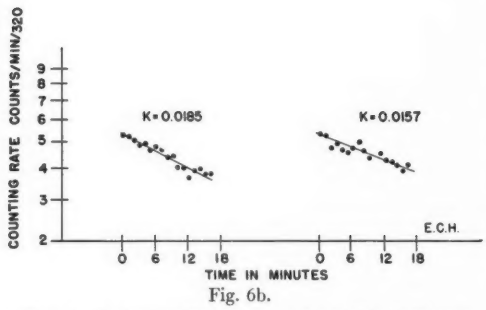

Fig. 6b.

Fig. 6. Patient E.H. with arteriosclerosis obliterans. a, Graph showing skin temperatures; b, graph representing rate of removal of sodium.

edema was confined largely to the subcutaneous tissues (Fig. 7).

Thromboangiitis obliterans (Buerger's disease). Five patients with thromboangiitis obliterans were studied. There was a variation in the degree and extent of the obliterative process in these individuals. In patients with symptoms confined largely to distal ulcerations on the toes and with good major arterial pulsations, the sodium disappeared rapidly from the gastrocnemius muscle. Patients with advanced disease demonstrated a slow removal of sodium chloride.

B.J.F. (Fig. 8.) One year prior to admission, this 53 year old white male developed intermittent claudications in the legs, which gradually increased in

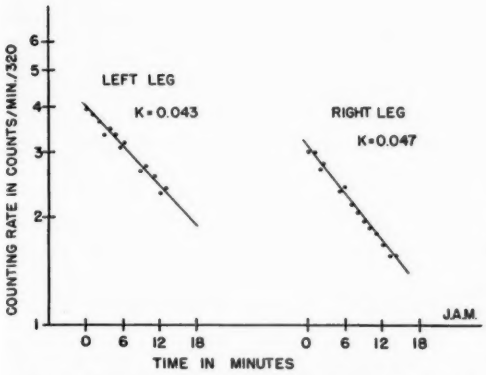

Fig. 7. Graph representing rate of removal of sodium in patient with chronic thrombophlebitis.

severity. Five months later this was followed by lesions of migratory phlebitis on the left forearm and the lower extremities. Six weeks prior to admission he developed pain and discoloration in the right great toe, and a small ulcer formed just beneath the great toenail.

Examination revealed cyanosis of the right great toe, with a small, painful ulcer on the terminal phalanx. Areas of migratory phlebitis were present on the left lower extremity and on the left forearm. Pallor of the right foot developed on elevation. Skin surface temperatures were normal. Oscillometry revealed essentially normal pulsations in the knee and ankle region. The dorsalis pedis pulsations were faint bilaterally. The posterior tibial pulsation was moderate on the left and absent on the right. There was a loss of hair over the toes on the right foot.

A diagnosis of thromboangiitis obliterans was made.

A right lumbar sympathectomy was performed, with removal of the sympathetic chain from the first to the third lumbar vertebra. There was immediate relief of pain in the foot, and improvement in the appearance of the ulcer.

DISCUSSION

To obtain constant results by this method of studying the mobilization of radioactive sodium chloride in the muscle, certain precautions must be carefully observed. The temperature and humidity in which the patient is studied should be constantly controlled. The procedure should be explained to the patient and his fears allayed regarding the discomfort associated with the procedure and the absence of danger from the use of radioactive materials. At the beginning of the study, extremities should be elevated for at least 10 minutes prior to the injection. The added strain imposed upon the circulation by the position of the extremity will thus become more completely manifest.

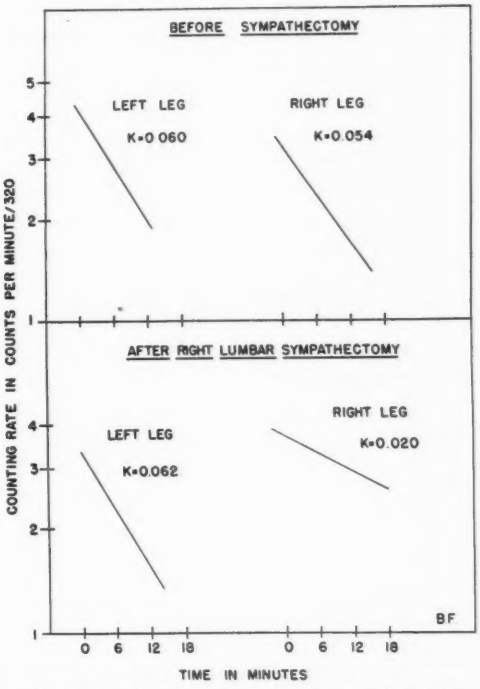

Fig. 8. Graph representing rate of removal of sodium in patient B.J.F. with thromboangiitis obliterans, before and after right lumbar sympathectomy.

The extremity must be carefully placed over the Geiger-Mueller tube and the position of the patient must be such that there will be no shifting of the body during the examination. It is obvious that variations in the distance of the injected deposit of sodium into the muscle from the Geiger-Mueller tube will in itself change the rate of count and will therefore produce artefacts in the determination. The patient must be constantly observed and reminded that the extremities should remain motionless; this is particularly important in elderly patients who unconsciously change the position of their legs. In individuals whose extremities become painful in the elevated position, these determinations must be carried out with the extremities horizontal.

More accurate determinations are obtained if small amounts of fluid are injected. It is necessary that the solution of sodium chloride be carefully prepared and be neutral in reaction.

SUMMARY AND CONCLUSIONS

By measuring the rate of disappearance of radioactive sodium chloride from the muscles of an extremity, an additional method of evaluating the circulatory physiology of the extremities has been made possible.

In the study of 57 normal individuals and 102 patients with peripheral vascular disturbances, curves representing the rate of disappearance of the sodium from the muscle form statistically accurate patterns.

It is believed that this method of study may offer a valuable aid in the evaluation of certain forms of therapy which are believed to enhance the circulation.

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SUTURE OF PERIPHERAL NERVES

Factors Affecting Prognosis

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ALL who have cared for patients in whose case a peripheral nerve has required suture know that complete recovery of function of the involved nerve does not always occur. Yet it also is known that under the proper circumstances an extremely gratifying recovery can ensue.

Careful selection of cases for neurorrhaphy, accurate operative technique, and good attention to the postoperative care of the patient all tend to produce conditions favorable for recovery. It would seem also that an understanding of the factors of importance in the prognosis of such injuries would lead to better treatment and thus ultimately to more nearly complete return of function than would otherwise be possible.

Because of this, we are recording an analysis of these factors obtained from a group of patients with peripheral nerve injuries during World War II. The literature in recent years has contained numerous reports on peripheral nerve injuries but it is felt that no useful purpose will be served by complete review of these. Instead, we are merely recording experience in one hospital in the hope that the data obtained from such a group of cases may be of value to others.

MATERIAL

Patients with peripheral nerve injuries, admitted to this army installation from September 14, 1942, to October 1, 1945, form the basis of this study. This group comprised 2,849 patients who had 3,276 injuries to peripheral nerves. For these nerve injuries, 957 neurorrhaphies were carried out, of which 673 were done by the members of the neurosurgical service at this hospital. The remainder were done at other army installations prior to admission of the patients to our hospital and the postoperative course was followed by us. Two hundred and seventy-nine neurolyses and 115 explorations without suture or neurolysis comprise the other operative procedures performed during this period at our installation.

The 957 neurorrhaphies were not all available for careful analysis and inclusion in this series. Cases were excluded if the neurorrhaphy was only partial; if we had no definite record or knowledge of the function present in the muscles innervated by the nerve in question prior to neurorrhaphy; and if the follow-up period was less than 6 months. After these cases were discarded 755 neurorrhaphies remained for careful analysis, and comprise the material analyzed for this study (Table I).

In each case, a record of the operative procedures and of the preoperative function present was available. Each patient was examined in so far as possible every 3 months during the follow-up period. The majority of patients were followed for 15 months although some were followed for as long as 28 months. Because the majority of patients were under observation for about 15 months the graphic presentation of the data includes the recovery occurring in the first 15 months after suture. Yet certain definite impressions of the recovery after 15 months were obtained and these will be recorded in the discussion as impressions.

In testing these patients for recovery of motor power, accurate palpation was employed to determine the extent of contraction of the muscle or of movement of its tendon. Due regard was paid to trick movements, substitution, anomalous innervation and the like. Motor power was graded arbitrarily in the following manner: grade 1 consists of a palpable degree of contraction or movement, of sufficient strength to produce movement of the part against gravity; grade 2, of a contrac-

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Work done on the Neurosurgical Service, O'Reilly General Hospital, Springfield, Missouri.

TABLE I.—SITE OF THE 755 NEURORRHAPHIES

Nerve*	Neurorrhaphies
Radial	129
Median	158
Ulnar	235
Musculocutaneous	8
Axillary	2
Sciatic	85
Peroneal	91
Tibial	23
Posterior tibial	10
Femoral	5
Sural	3
Total	755

*Brachial plexus injuries tabulated under component in question; for example radial, median, axillary, and so forth.

tion of sufficient strength to exert full useful movement against gravity; grade 3, of a contraction of sufficient strength to exert motion against strong resistance by the examiner; and grade 4, of a contraction of normal strength.

In the examination for the return of sensory function, only the area of smallest autonomous supply was examined, in order to eliminate in so far as possible the factor of overlap of sensory function. In the determination of return of sensory function, again a method of grading was employed as follows: Sensory function was considered to be grade 1 when firm, heavy pressure in the autonomous zone produced deep pain and light stroking of this area did not produce any sensation; grade 2 when light stroking of the autonomous zone by an object, such as a lead pencil or the examiner's finger produced a crude, tingling, usually poorly localized, sensation; and grade 3 when light touching of the autonomous zone produced actual tactile sensation. In this last grade further tests were made for the presence of the following: (1) perception of heat and cold; (2) perception of light touch, as with a wisp of cotton; (3) perception of a sharp pin prick as opposed to the stimulus of a dull object; (4) stereognosis; and (5) two point discrimination.

In the discussion from this point on, we shall designate as "recovery" only motor function of grade 2 or more. Thus, when it is stated that 50 per cent of patients had recovery in a given muscle, it is meant that this group had at least function of grade 2 in this muscle. An additional group may have had function of grade 1 but no data with regard to this will be included. In discussing sensory recovery we shall refer to recovery of function of grade 1, 2, or 3 without further breakdown of recovery of function of grade 3.

METHOD OF ANALYSIS OF DATA

In order to study the effect of various factors, the cases were grouped into the subdivisions desired for each analysis. Thus, for example, in order to determine the effect of the level of injury, the instances of radial neurorrhaphy were grouped according to the level of injury of the nerve. Each group was then analyzed in order to obtain the percentage of patients with recovery of each muscle innervated by this nerve at certain intervals after operation. A graphic comparison of the data was then constructed.

Certain factors made the statistical problem somewhat complicated. In the first place some individuals were examined, let us say, 3 months, 6 months, and then not again until 12 months after operation. Others may not have been examined until 9 months after suture as their first postoperative check. Thus each of the individuals in a given group may not have returned at *each* examination time; thus the time required for recovery was not determinable in some cases although it might be known in such cases that recovery had taken place at say 12 months after suture. It was thus impossible to record literally the percentage of the group who had recovered in each interval of 3 months after suture by direct observation. This is similar to the problem of calculating survivals after surgical treatment for malignant disease. The individuals available for observation at different periods after surgery may not be the same because some are lost track of in the course of years. Fortunately, the method for dealing with this statistical problem has been worked out (1) and can be applied with accuracy sufficient for the present purpose.

The essence of the method consisted of determining the percentage of individuals recovering within any period after operation. This is accomplished by considering, of the total number examined at the end of a given interval (say 9 months after suture), only those known not to have recovered at the end of the previous interval (in this instance 6

months after suture). From this group, one is able to determine by examination the number who have recovered function during this latter period and thus the specific recovery rate for the interval can be calculated. The application of such rates calculated for each interval in an appropriate manner gives the desired accumulated recovery rate.

The essentials of the method are basically very simple. As an example, they will be presented here briefly in terms of the experience with radial neurorrhaphy, analyzed according to the interval between wounding and suture. For purposes of illustration, the calculations necessary for construction of the curve for those cases sutured from 4 to 6 months after injury when recovery of the extensor carpi radialis longus muscle only is considered, are presented.

These calculations are given in Table II. Fifty-one individuals were examined 6 months after suture who were known not to have recovered at 3 months after suture; of these 20 were found to have recovered. The recovery rate for the interval 3 to 6 months therefore was 39.2 per cent. Twenty-seven individuals were examined 9 months after suture who had not recovered at the 6 months' point[1] and of these 14 had recovered; this gives a rate of 51.8 per cent for the interval 6 to 9 months. Similarly the interval recovery rates for the 9 to 12 and 12 to 15 month periods were found to be 10 per cent and 80 per cent respectively.

With the interval recovery rates so ascertained we proceeded with the calculation as shown in columns 4 to 7 of Table II. We begin with a hypothetical 1,000 individuals who had not recovered at the end of the zero to 3 month period. Of these, 39.2 per cent recovered during the interval of 3 to 6 months (column 5) obtained from column 3, or 392 have recovered in the interval (column 6), leaving 608 (column 4) who had not recovered at the beginning of the 6 to 9 month interval, so that 39.2 per cent (column 7) have recovered by the beginning of that interval. Of the 608 individuals who had not recovered at the beginning of the 6 to 9 month interval, 51.8 per cent recovered during the interval, that is, 315, leaving 293 (column 4) who had not recovered at the beginning of the 9 to 12 month interval; therefore 707, or 70.7 per cent (column 7) have recovered by then. The continuation of this process completes Table II. In this manner are determined the percentage of persons recovered at various periods after suture as given in column 7. The course of recovery then can be shown graphically by plotting the accumulative percentage of persons recovered (column 7) against time (Fig. 1).

TABLE II.—EXAMPLE OF CALCULATION OF TIME-RECOVERY CURVE FOR RADIAL NEURORRHAPHY PERFORMED 4 TO 6 MONTHS AFTER INJURY: RESULTS OBTAINED IN EXTENSOR CARPI RADIALIS LONGUS MUSCLE

From observations				Calculation of curve			
1	2	3		4	5	6	7
Interval since suture of nerve, mo.	Patients examined with *no* recovery at beginning of interval	Recovered in interval		Patients without function at beginning of interval	Interval recovery rate, per cent	Patients recovered in interval	Per cent recovered by beginning of interval
		No.	Per cent				
3-6	51	20	39.2	1,000	39.2	392	0
6-9	27	14	51.8	608	51.8	315	39.2
9-12	10	1	10.0	293	10.0	29	70.7
12-15	5	4	80.0	264	80.0	211	73.6
15+				53			94.7

The construction of each curve of recovery necessitated such a calculation and table. In order to conserve space, however, none of the other tables are included in this paper.

An attempt was made when studying a given factor, such as the wrapping of the suture line with tantalum foil, to utilize a homogeneous group of cases. Thus when using the cases of radial neurorrhaphy to study this factor, individuals were selected whose nerves were sutured within 9 months after injury and whose lesions were located from 0 to 12 centimeters proximal to the lateral epicondyle; this group was then divided into those in which the nerves had been wrapped in tantalum foil and those in which they had not been wrapped in tantalum foil. The legend for each graph will indicate the method of selection of cases.

In the remainder of the paper the data are presented in their entirety in the graphs. No

[1]Note that this is the number of patients examined 9 months after suture who had not recovered 6 months after suture, *not* the total number of patients examined 9 months after operation.

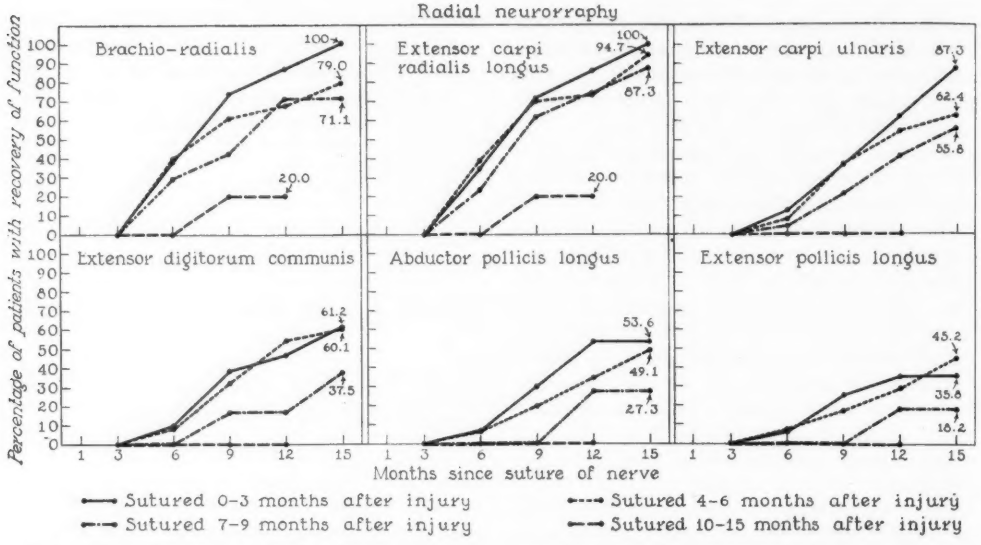

Fig. 1. Effect of the interval elapsing between wounding and suturing on the recovery of motor function after radial neurorrhaphy has been performed. All cases are covered in the graphs.

lengthy discussion of these data will be undertaken, but only a summary of their significance will be given.

THE EFFECT OF INTERVAL BETWEEN INJURY AND SUTURE

Motor function. The effect of the interval between injury and suture on the return of motor function was studied after suture of the radial and ulnar nerves had been performed (Figs. 1 and 2).

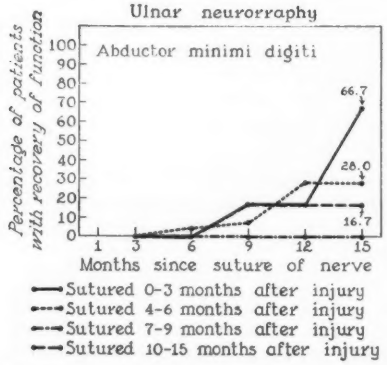
Ulnar neurorraphy
Abductor minimi digiti
Percentage of patients with recovery of function
Months since suture of nerve
Sutured 0-3 months after injury
Sutured 4-6 months after injury
Sutured 7-9 months after injury
Sutured 10-15 months after injury

Fig. 2. Effect of the interval between wounding and suturing on the recovery of function in the abductor minimi digiti muscle after ulnar neurorrhaphy. Only cases in which the lesion was located 5 centimeters or more distal to the medial epicondyle were included.

It is obvious that suture of divided nerves within 3 months after injury gives superior results. Nerves which have been sutured after 3 months, but not more than 9 months, have elapsed, show a reasonable amount of recovery. Furthermore, large muscles, for example the extensor carpi radialis longus, seem to do nearly as well when the nerve is sutured within 9 months after injury as they do when it is sutured after only 6 months have elapsed. However, the return of function in the small and more distally placed muscles, such as the extensor digitorum communis or the extensor pollicis longus, is distinctly less good when the nerves supplying them have been sutured from 7 to 9 months after injury, rather than earlier.

That early suture is of greatest importance when return of function in small muscles is desired is further illustrated by the data obtained from a study of suturing of the ulnar nerve in the forearm (Fig. 2). The observations on the abductor minimi digiti show clearly that repair within 3 months after injury is highly desirable.

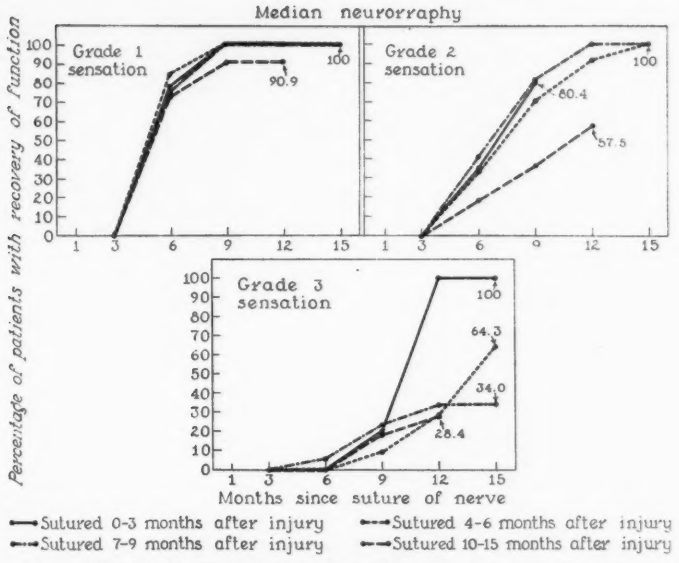

Fig. 3. Effect of the interval between wounding and suturing on the recovery of sensory function after median neurorrhaphy. Only cases in which the lesion was located 5 centimeters or more distal to the medial epicondyle were included.

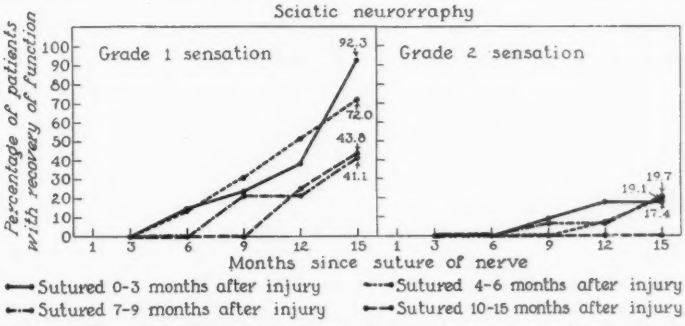

Fig. 4. Effect of the interval between wounding and suturing on the recovery of sensory function after sciatic neurorrhaphy. All cases. There were no instances of recovery of sensory function of grade 3.

When the divided nerve is sutured 10 to 15 months after injury, the results are distinctly inferior. Nonetheless, since 20 per cent of the patients were able to regain active extension of the wrist even when 10 to 15 months had elapsed between injury and suture of the radial nerve, suture is worth while in this situation even at that late date. However, when it is done as late as 10 months after severance of the nerve, it must be realized that a certain portion of the motor deficit most probably will have to be compensated for later by an appropriate transference of tendons.

Sensory function. In the median nerve (Fig. 3), and also in the ulnar nerve, although the data are not presented, a sensory return of grade 1 can nearly always be expected if the nerve is sutured within 9 months after injury. As a matter of fact, 90 per cent of the patients obtained this much return of function when

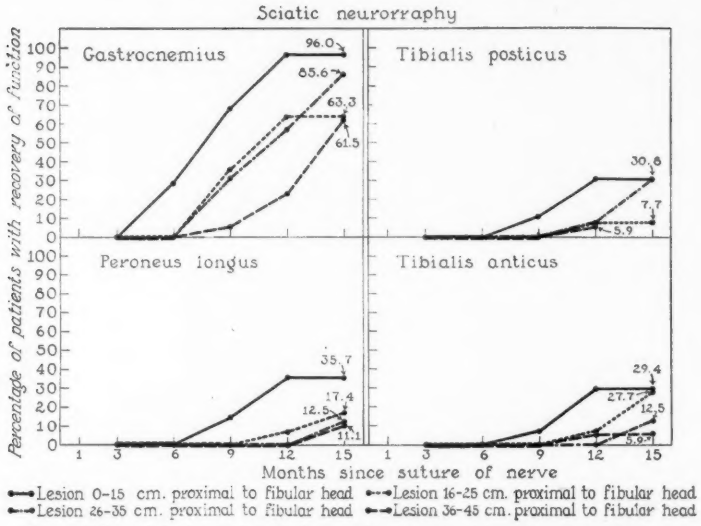

Fig. 5. Effect of the level of the lesion on the recovery of function after sciatic neurorrhaphy. Only cases in which the nerve was sutured within 15 months after injury were included.

the nerve was sutured as late as 15 months after injury. Sensory return of grade 2 likewise ensued in nearly all instances when the nerve was sutured within 9 months of its severance. In more than half of the cases in which the nerve was sutured from 10 to 15 months after injury such a return occurred. There is no doubt, however, that suture within 3 months of injury is of unquestioned superiority in obtaining a return of sensory function to grade 3 in the median and ulnar nerves. Yet the return of nearly normal sensation with stereognosis and two point discrimination is uncommon even under these favorable circumstances.

In the sciatic nerve (Fig. 4) return of sensory function in general was disappointing in our experience. There were no instances of sensory return of grade 3. Suture within 3 months gave slightly less than 20 per cent of the patients so treated return of sensory function to grade 2 which is indeed disappointing. Suture at any time within 9 months gave just about this same result. The postponement of suturing beyond this date gave uniformly unsatisfactory results. It might further be added that the long term follow-up, in some cases for 28 months after suture of the nerve, has substantiated these observations that a return of sensory function to grade 3 in the sciatic nerve, even under the best of circumstances, is indeed rare.

EFFECT OF THE LEVEL OF THE INJURY

Motor function. The data for the sciatic nerve are presented in Figure 5. The conclusions drawn from these data were substantiated by data calculated for the other nerves, which we are not presenting.

It is obvious that in general a higher percentage of patients with distally placed lesions, than of those with more proximally located injuries, recover. However, even lesions high in the sciatic nerve did allow some motor recovery in many instances. The same is true of lesions high in the nerves of the arm, that is lesions of the brachial plexus and cervical nerve roots.

Thus, in patients with high-lying lesions, a special effort should be made to obtain end-to-end anastomosis within a few months after injury so that the best possible recovery under the circumstances will ensue.

Sensory function. The data with regard to sensory recovery are obtained from a comparison of two groups of median nerve in-

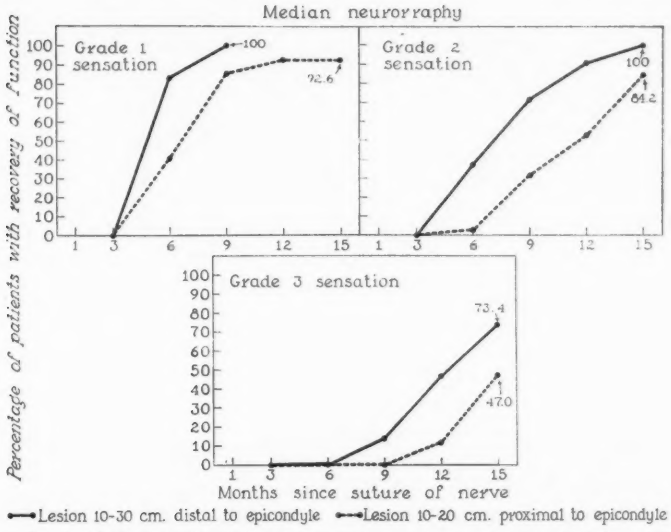
Median neurorraphy
Grade 1 sensation
Grade 2 sensation
Grade 3 sensation
Percentage of patients with recovery of function
Months since suture of nerve
Lesion 10-30 cm. distal to epicondyle
Lesion 10-20 cm. proximal to epicondyle

Fig. 6. Effect of the level of the lesion on the recovery of sensory function after median neurorrhaphy. Only cases in which the nerve was sutured within 6 months after injury were included.

juries, both sutured within 6 months after injury (Fig. 6). One group comprises patients with lesions at certain levels in the forearm, while the other comprises those with lesions at certain levels in the arm.

Return of sensory function of grade 1 and grade 2 was slightly superior for the low-lying lesions to that for high-lying lesions. It would appear also that the low-lying lesions have a superior return of sensory function to grade 3. However, since both curves were continuing to rise at the last period plotted, these data are not entirely convincing. The patients whom we have seen as long as 28 months after injury, however, have given us the impression that this is a true difference.

Mention has been made of the poor prognosis for return of sensory function in cases of injury to the sciatic nerve. Thus the prognosis is unusually poor for recovery of sensory appreciation in high-lying lesions of this nerve.

EFFECT OF GAP BETWEEN NERVE ENDS AFTER RESECTION OF NEUROMA AND GLIOMA

These data are presented only with regard to return of motor function. Two groups of cases, namely those in which median neurorrhaphies (Fig. 7) and sciatic neurorrhaphies (Fig. 8) were performed will be considered. Without belaboring the differences that do occur, it can certainly be stated without hesitation that the presence of a large gap between the nerve ends is no barrier to *at least* partial recovery of function, if careful suturing has been carried out. Thus we feel strongly that large gaps should never deter the surgeon from carrying out an end-to-end anastomosis if such is at all feasible, for in such cases he will frequently be rewarded by a gratifying recovery of motor function.

EFFECT OF THE WRAPPING OF THE SUTURE LINE WITH TANTALUM FOIL

Motor function. A difference of opinion occurred among the surgeons caring for these patients concerning the value of the wrapping of the suture line with tantalum foil. Consequently, two fairly comparable groups of cases are available, in one of which wrapping of the suture line was employed and in the other of which it was not employed. The data obtained from an analysis of radial neurorrhaphies are given in Figure 9 and those from an analysis of sciatic neurorrhaphies in Figure 10

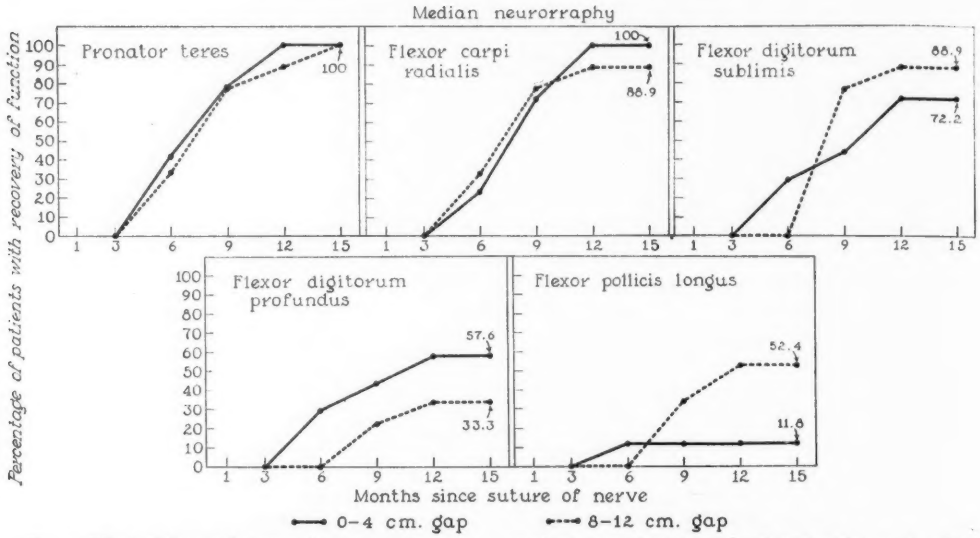

Fig. 7. Effect of the gap between the nerve ends on the recovery of motor function after median neurorrhaphy. Only cases in which the lesion was located from 0 to 15 centimeters proximal to the medial epicondyle and in which the nerve was sutured within 6 months after injury were included.

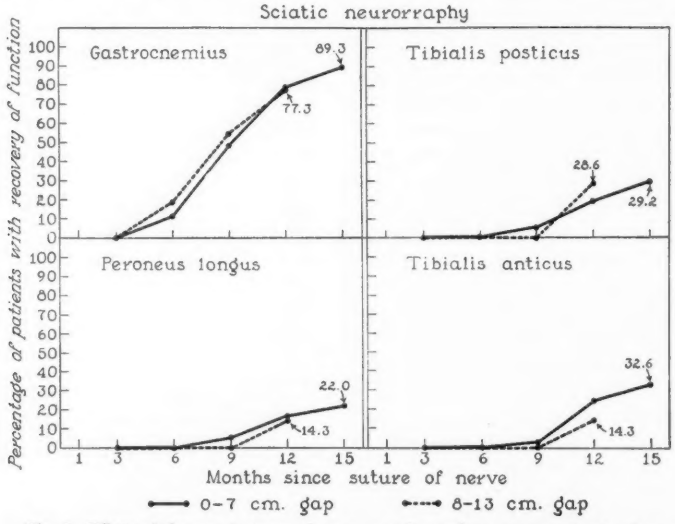

Fig. 8. Effect of the gap between the nerve ends on the recovery of motor function after sciatic neurorrhaphy. Only cases in which the lesion was located from 0 to 35 centimeters proximal to the head of the fibula and in which the nerve was sutured within 9 months after injury were included.

with regard to the effect of this factor on the recovery of motor function.

It seems fair to conclude that the employment of a wrapping of tantalum foil does not improve the results of neurorrhaphy. Furthermore, these data indicate that the patients in whom tantalum foil had been used actually did less well than the group in which it had

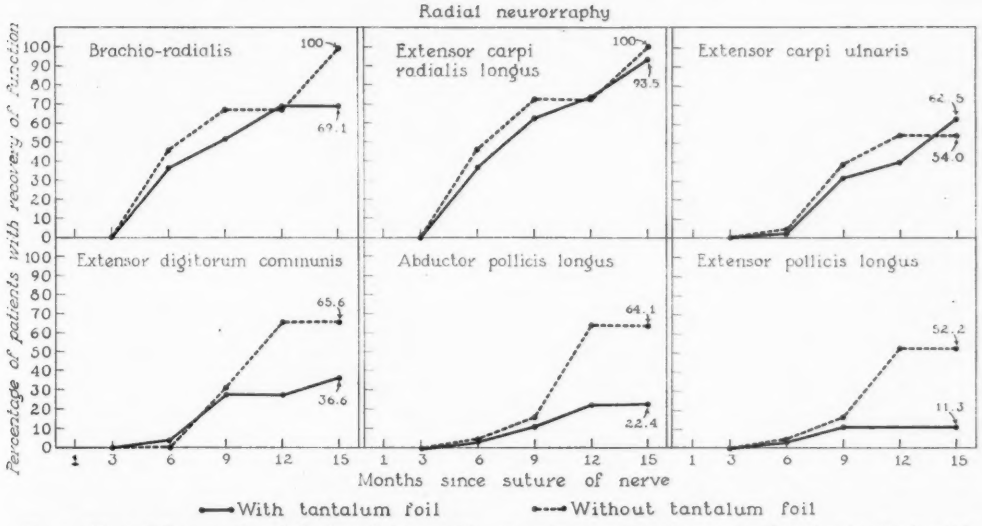

Fig. 9. Effect of the wrapping of the line of suture with tantalum foil on the recovery of motor function after radial neurorrhaphy. Only cases in which the lesion was located from 0 to 12 centimeters proximal to the lateral epicondyle and in which the nerve was sutured within 9 months after injury were included.

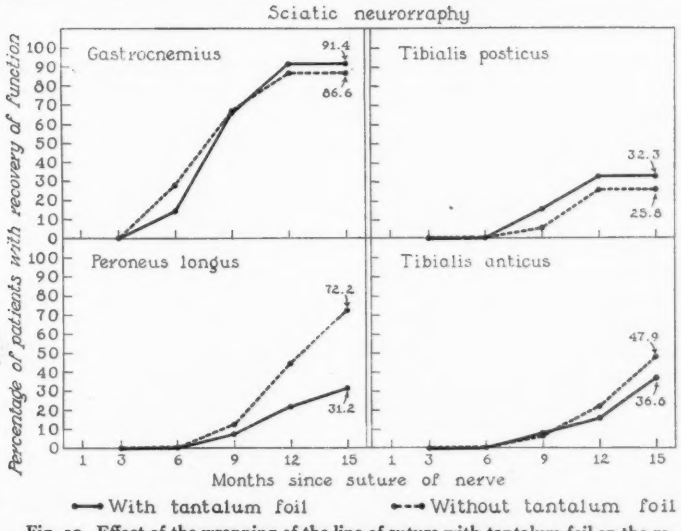

Fig. 10. Effect of the wrapping of the line of suture with tantalum foil on the recovery of motor function after sciatic neurorrhaphy. Only cases in which the lesion was located from 0 to 25 centimeters proximal to the head of the fibula and in which the nerve was sutured within 6 months after injury were included.

not, particularly with regard to the return of function in smaller and more distally placed muscles, such as the abductor pollicis longus and extensor pollicis longus muscles.

Sensory function. The data on median neurorrhaphies in the forearm (Fig. 11) and sciatic neurorrhaphies (Fig. 12) are presented to illustrate the effect of wrapping on recovery of

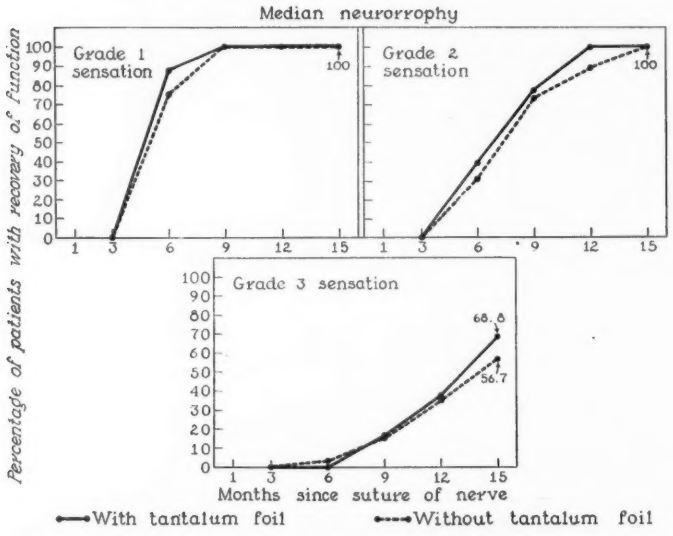

Fig. 11. Effect of the wrapping of the line of suture with tantalum foil on the recovery of sensory function after median neurorrhaphy. Only cases in which the lesion was located from 5 to 30 centimeters distal to the medial epicondyle and in which the nerve was sutured within 9 months after injury were included.

sensory function. These data suggest no great difference in recovery between the cases in which wrapping had been employed and those in which it had not been employed. There would appear to be a slight superiority of return to sensory function of grade 3 in the median nerve when wrapping is employed, but it is doubtful if this is of significance.

Comment. It can thus be concluded that wrapping of the suture line with tantalum foil has no discernible advantages. In addition to the absence of any demonstrable effect on end-results, the use of tantalum foil in this manner seems of doubtful value on the basis of the appearance of the suture line in the nerve at re-exploration. Many surgeons have commented on the fact that such anastomoses in nerves often appear attenuated and compressed by a constricting cuff of tantalum foil.

EFFECT OF THE MICROSCOPIC APPEARANCE OF THE RESECTED ENDS OF THE NERVES

It was the practice at this neurosurgical center to examine microscopically the cut ends of segments removed from the nerves prior to anastomosis. In this manner, examination of the mirror image of the approximated nerve ends was made. The presence of any neuroma in the proximal end of the nerve or of any glioma in the distal end was ascertained. Further note was made of the presence of shrinkage of the tubules of Schwann's cells, of edema of the funiculi, and of fibrosis and cellular infiltration of the nerve trunks.

Because it was also our practice to obtain frozen sections at the time of operation on all questionable nerve ends, we fortunately had a very small number, 24 in this series, of cases in which operation was performed in this installation and in which the permanent sections showed "unsatisfactory" nerve ends. In 17 cases a neuroma occupied half or slightly more of the proximal end of the nerve. In 7 cases glioma occupied half or more of the distal end; in 1 of these 7 cases the glioma occupied almost all of the end of the nerve.

A statistical analysis of such a small group is, of course, impossible. A study of the recovery in these cases does allow a few statements however. In the cases in which half or slightly more of the end of the nerve consisted of neuroma, a definite return of function oc-

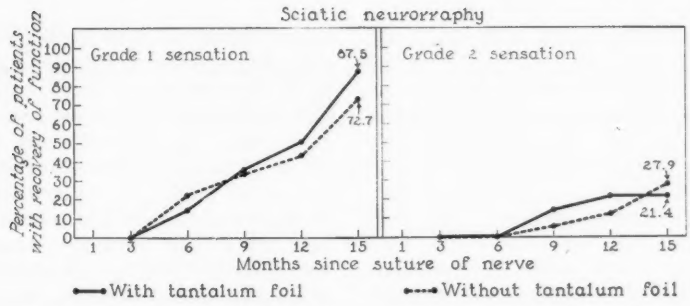

Fig. 12. Effect of the wrapping of the suture line with tantalum foil on the recovery of sensory function after sciatic neurorrhaphy. Only cases in which the lesion was located from 0 to 25 centimeters proximal to the head of the fibula and in which the nerve was sutured within 6 months after injury were included. There were no instances of recovery of sensory function of grade 3.

curred, but in only 3 did a really good recovery occur. Thus it may be fairly concluded that in cases such as this, some, although incomplete, return of function may be expected. In only 1 of the 6 cases in which half of the end of the nerve was glioma could the recovery of function be classified as of good quality. In the 1 case in which the distal end was nearly all glioma no return of function occurred.

We thus feel that it is essential to obtain good funiculi both proximally and distally even if this entails the production of a considerable gap between the ends of the nerve. Such a gap of course usually can be overcome by careful and extensive mobilization of the nerve. If it becomes apparent that despite these measures sufficient nerve cannot be resected to give two healthy ends, an occasion which should be unusual, then the distal end should be resected until good funiculi are seen; the proximal end then should be resected back as far as possible. When on such occasions good funiculi cannot be obtained on the proximal end of the nerve some recovery, although usually incomplete, can be expected.

EFFECT OF OTHER FACTORS

Tension on completed anastomosis. We were not able to obtain statistical data on this factor. Nonetheless, it is our distinct impression, gained during the experience of operating on and caring for these patients and substantiated by a careful review of all of their records, that some tension on the suture line does not endanger the functional result. As a matter of fact, we have frequently seen cases in which the suture line was under much tension and yet a good recovery of function ensued.

It is obvious that extreme tension on a suture line is not desirable, primarily because it imposes the risk of disruption. In certain instances in which considerable nerve is either lost or damaged, however, it is impossible despite all efforts to effect neurorrhaphy without such tension. If the mobilization has been extensive, if sutures are accurately placed in the tough epineurium, and if the postoperative immobilization has been properly done, disruption of the anastomosis, even when under considerable tension, is rare. We are of the opinion that it is preferable to resect the nerve back to good nerve ends and to have the anastomosis under considerable tension than it is to resect less nerve in order to have the anastomosis only under slight tension, but then to have neuroma or glioma in the sutured nerve ends.

Whenever possible, of course, the operation should consist of resection of the nerve back to good ends, and the establishment of an accurate anastomosis under only slight tension.

Suture material. It was not possible to analyze the data in such a way that the influence of one or another type of suture material could be ascertained. However, we wish to record a few impressions.

It is highly probable that any fine nonabsorbable suture material, such as silk, cotton,

tantalum wire, or steel wire, will yield excellent results. It is important, however, to use at least a few radiopaque sutures in some manner on the ends of the nerve so that a subsequent roentgenogram will yield information concerning the presence or absence of disruption of the suture line. The importance of a careful check of this in each case cannot be overemphasized.

It did not seem possible to ascertain from our data the effect of the use of a stay suture. On theoretic grounds, however, we believe such a suture is not advisable and we have rarely employed it.

COMMENT

These data lend factual confirmation to the results of many previous studies, and also the impressions of many who have managed peripheral nerve injuries. Complete recovery of function, to a degree comparable to the normal state, is indeed rare after nerve suture. Eminently satisfactory recoveries, however, can be obtained in many instances.

The patient's interests are best served by accurate end-to-end anastomosis of the nerve within 3 months after injury and preferably in the first month after injury. High-lying injuries, such as those of the brachial plexus, should be an especial stimulus to early repair. However, repair is of value, though limited, when done as long as 15 months after injury. Beyond this period, motor recovery will rarely result but some return of crude sensory function may occur.

Large gaps between the healthy portions of a divided nerve offer a temptation to the surgeon to deem the lesion inoperable, or to perform bulb suture with the hope of subsequent resection and suture. Such extensive injuries do undoubtedly influence unfavorably the end-results even if an anastomosis is obtained. Nonetheless, good results can frequently be obtained in these cases if the surgeon is prepared and willing to undertake an extensive dissection of the nerve in order to make union of healthy ends possible. Despite some encouraging results (2) the superiority of the use of autogenous nerve grafts over end-to-end anastomosis of the divided nerve in such situations has not been conclusively demonstrated.

No advantage is served by the wrapping of the line of anastomosis in tantalum foil. A few metallic sutures at appropriate points in the nerve ends are of value in that they allow the surgeon to assure himself that the anastomosis is still intact at any time in the postoperative period.

The surgeon must not be discouraged at any time during operative procedures on peripheral nerves, for it is usually possible to effect a satisfactory neurorrhaphy. At the same time, he should not be overoptimistic during the months which follow, since certain factors may preclude a nearly complete recovery in a given instance. He should recognize these factors, and be ready to recommend or perform suitable reconstructive procedures at an appropriate time. This broad view makes available to the patient the best that surgery can offer.

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STRATIFICATION OF BILE IN THE GALL BLADDER AND CHOLELITHIASIS

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THERE is a voluminous literature on the composition of bile in the gall bladder and on the concentration function of that organ, which can be found from recent reviews (8). In these reviews it is implied, though not stated, that the contents of the gall bladder, at any one time, can be thought of as homogeneous, so that a sample of bile from any part of the bladder would be representative of the whole.

Yet roentgenological evidence, from several investigators (2, 3, 4, 5, 6, 9), has long been published, which indicates, to the contrary, that a high degree of inhomogeneity of bile may exist in the human gall bladder in normal subjects as well as in cholecystitis. Roentgenograms show that the bile in lowest part of the bladder often has a markedly greater radio-opacity than that above, with one or more sharp lines of demarcation between.

When "floating" gallstones are present, these are often found to lie in this region of apparent separation between two layers. It is necessary to roentgenograph the patient in an upright, rather than in the usual horizontal, position to reveal these phenomena (Fig. 9). Bernstein (2) has put forward a theory of the origin of this "stratification" and suggested its connection with the formation of gallstones. A review on the roentgenological evidence by Bernstein is in course of publication.

However, there have been critics (Akerlund) who have maintained that the introduction of iodized oil, needed to visualize the layers, leads to artefacts which are wholly responsible for the phenomena observed. It is of obvious importance that our concept of the state of the bile in the gall bladder should include "stratification," if this is physiologically present, so, at the suggestion of Dr. Bernstein, it was decided to seek evidence, other than roentgenological, on the point.

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METHODS

The obvious line of attack was to secure samples of bile from different levels in the gall bladders of animals and if possible from those of patients at cholecystectomy, and to examine them to see if differences existed at different levels. Measurements of specific gravity of the samples, which can easily be made with only a few drops, offered the best starting point. Measurements of viscosity, indicative mainly of the amount of mucoid material, of hydrogen ion concentration, and of a "color index" were later added.

Technique of obtaining samples. As far as the choice of an animal was concerned, it was felt that one in which gallstones occurred naturally would be most suitable. In answer to a request for information, the Ontario Agricultural College replied that among the common experimental animals, gallstones occurred so infrequently as to be practically nonexistent, though among the domestic animals beef cattle had such stones more frequently than other species. It is of interest that in 1 such animal a "cholesterol" stone was found in the gall bladder during this research.

Preliminary experiments were made upon the gall bladders of cats which became available. These cats had been used in acute experiments in which various convulsive drugs were given. As soon as the animal had been killed, the gall bladder was removed from the body and suspended with the fundus hanging down in order that samples might be taken. Five-tenths cubic centimeter samples of bile were then drawn off by means of a hypodermic needle, at intervals of 1 centimeter from one another, from the neck down to the fundus of the gall bladder. The uniformity of the distance between the levels of the samples was gauged by suspending the bladder beside a ruler and steadying it there. When possible, samples were also drawn from the hepatic ducts.

The results in the cat series, given in detail later, were by no means conclusive due to the small size of the bladder and the consequent difficulty in obtaining accurately spaced samples of adequate size.

Gall bladders of cattle proved to be more suitable for the purposes of this experiment. In length from neck to fundus, they average about 12 centimeters (7 to 19 cm.). Because of their large size, it is possible to draw off relatively large samples (2 c.c.), accurately spaced, without interfering greatly with any stratification which may be present. The gall bladders were obtained at a local abattoir from beef cattle which were to be killed and the meat dressed for sale. A 48 hour period of fasting preceded the death of the beasts which were 2, 3, and 4 year old heifers for the most part, with the occasional bull and cow. It was subsequently appeared that sex and parity in no significant way affected the results obtained. The method of killing is worthy of note. The beast was first driven into a small pen just large enough to hold it, the floor of which was a trap door. It was stunned with a blow on the forehead whereupon the trap door was opened and the animal dropped, or rather rolled, to the killing floor 3 feet below. During this drop, the animal was completely turned over so that the gall bladder presumably experienced a considerable amount of disturbance. The actual killing was accomplished by severing the aorta and allowing the animal to bleed to death. A certain amount of struggling marked the death of most of the animals. The animals used in the experiment were completely unselected, being taken as they came, in order to obtain a representative series on essentially normal beasts. From the time the animal was killed until samples were drawn, was, on the average, about 15 minutes (7 to 25). As soon as the bladder was freed from the body, it was suspended beside the ruler, fundus down, and samples were withdrawn at centimeter intervals. The needle of the syringe was introduced through the wall, bevel upward, as close to the vertical axis of the bladder as possible.

In addition, a small series of cases in humans was investigated. These were all patients with clinical cholecystitis and cholelithiasis. The method of obtaining samples will be discussed in a separate section.

Technique of measurements made on samples. The specific gravities were measured by testing whether a drop of the bile floated or sank in solutions of known specific gravity. The known solutions, in this case, were mixtures of bromobenzene and xylene, the relative proportions of which were varied to give a series of solutions of known specific gravity ranging from 1.000 to 1.080 in steps of .005, that is to say 1.000, 1.005, 1.010, and so on. By mixing two of these solutions in equal quantities solutions of intermediate specific gravities were obtained (i.e. measurement was made in steps of .0025 in specific gravity).

The viscosity of the samples was measured by a microviscosimeter of the Ostwald type in which the capillary tube and bulb of a white blood cell pipette was used. The measurement consisted of placing a known quantity of bile, 0.5 cubic centimeter, in the viscosimeter and, by means of a stop watch, measuring the length of time it took to pass through the capillary tube. Results are relative rather than absolute.

In a small series of bladders the color index of the bile was measured as well as the specific gravity. The measurement was made by comparison, in a visual comparison colorimeter (Hellige), of the unknown with a standard solution. Two-tenths cubic centimeter of bile was diluted to 10 cubic centimeters and the comparison was made of this solution with the standard, which was 1:10,000 potassium dichromate solution.

The hydrogen ion concentration was also determined by means of a standard electrometric apparatus.

Alternative method of investigating stratification. A gall bladder obtained in the usual way was suspended over a large graduated cylinder. A small bore hypodermic needle was introduced through the lowest part of the bladder and the bile was allowed to drip out through the needle and run slowly down the side of the graduate. When the bladder had been completely emptied, samples were taken at regular intervals, with a pipette introduced to different depths. Specific gravity determinations were made after a period of 4 hours, and

TABLE I.—RESULTS

Amount of difference in specific gravity	No. of bladders	Percentage
No change (less than .0025)	11	17
.0025	15	23
.0050	12	18
.0075	5	8
.0100	7	11
.0125	1	2
.0150	3	4
.0175	5	8
.0200	4	6
.0225	2	3
Greater than .0225	0	0
Total	65	100

on samples taken each succeeding 24 hours for 1 week.

RESULTS

Gall bladders of cats. The results obtained in these experiments were suggestive but the series is too small to have any statistical significance. In all, 8 cat gall bladders were investigated by the technique previously described. It was possible to draw off at least 4 samples at centimeter intervals for examination.

Figure 1 shows the results of the specific gravity measurements in 1 of these cat gall bladders. Of the 8 bladders, 4 showed changes in specific gravity, from the neck to the fundus of the bladder, larger than could be accounted for by experimental error. Three of these 4 bladders gave evidence of stratification, that is to say, abrupt changes of specific gravity as in Figure 1. In the cases in which it was possible to obtain a large enough sample of bile from the hepatic duct to examine, it was found to be much less concentrated (specific gravity 1.015-1.020) than the bile of the bladder (specific gravity as high as 1.045).

Gall bladders of cattle. In Table I, the results in a series of 65 animals are analyzed according to the difference found in specific gravity between samples drawn from the uppermost and the lowest levels. It will be seen that in 54 of the 65 bladders there was a difference between top and bottom certainly greater

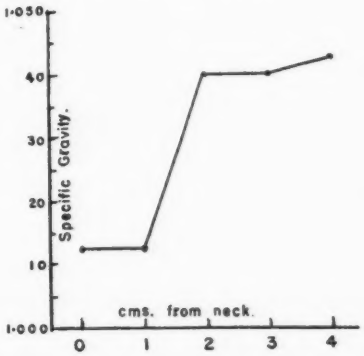

Fig. 1. Specific gravity at different levels in the gall bladder of a cat, indicating two "strata."

than the least difference measurable, and in a large number of bladders the difference was much greater. From this table it is concluded that a considerable degree of inhomogeneity of the contents of the gall bladder of cattle is the rule rather than the exception.

Table I makes no distinction between those cases in which the change from top to bottom was gradual, or at least in steps so small as to be within the error of measurement, and those in which a sudden sharp increase in specific gravity between adjacent samples was found (as in the cat gall bladder of Fig. 1). There were 8 cases in which a sharp increase of .0050 in specific gravity was present, 1 of .0075, and 4 of .0100, as well as 6 more cases in which "stratification" was probably present. An example in which stratification undoubtedly exists is shown in Figure 2. Moreover, there were cases in which there was more than one

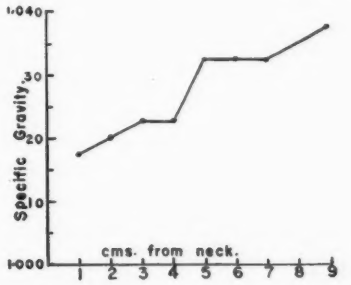

Fig. 2. Stratification in specific gravity in the gall bladder of a heifer.

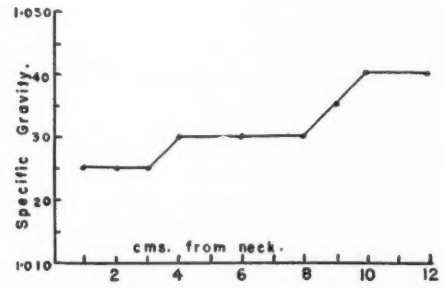

Fig. 3. Results in the gall bladder of a heifer indicating three distinct strata.

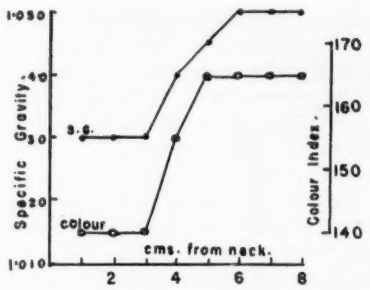

Fig. 4. Relation between specific gravity and intensity of color at different levels in gall bladder of a heifer.

sharp increase in specific gravity, indicating several strata in the same gall bladder, as in Figure 3.

A significant observation was that in all cases in which there was no difference in specific gravity between top and bottom of a gall bladder, the specific gravity was throughout very low, equal to that usually found in the neck (i.e. less than 1.020).

In the original work of McMaster and Rous (10) on the concentrating ability of the gall bladder, the pigment concentration was taken as the criterion of concentration. In view of this, both specific gravity and a color index were measured at different levels in 6 bladders. The results indicated a very close correlation (Fig. 4.).

Estimations of the viscosity of the bile were done on 35 bladders. These included 22 immediate samples, 8 twenty-four hour samples, and 5 forty-eight hour samples. Specific gravity determinations were made at the same time. It was found that the viscosity bore little relation to the specific gravity, though generally speaking, the viscosity appeared to increase as the fundus of the bladder is approached. This is more noticeable in the later than in the immediate samples. Viscosities were very variable ranging from 1.4 to 5.0 times that of water, with a mean of 2.1 times the viscosity of water.

It was expected that the hydrogen ion would be among the most diffusible of substances and that the hydrogen ion concentration of the bile would be constant throughout the gall bladder, even when there was a "stratification" in specific gravity and in concentration of pigments.

Contrary to expectation, the results of this investigation show that the *p*H values in a given bladder are closely correlated with the specific gravity. The bile becomes more acid the greater its concentration. This fact has been long known to apply to representative samples from a gall bladder as concentration proceeds (9), but here it is shown that the relation holds for simultaneous layers in the same gall bladders (Fig. 5). Moreover, 24 hour specimens showed no essential change from those which had preceded them. The *p*H values confirm the finding, given by the

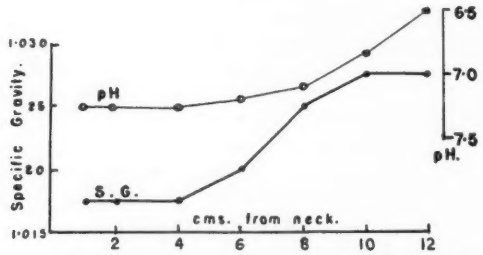

Fig. 5. Relation between specific gravity and hydrogen ion concentration in gall bladder of a heifer.

TABLE II.—CHANGE IN THE DIFFERENCE OF SPECIFIC GRAVITY TOP TO BOTTOM WITH TIME OF STANDING

No. of bladders	Mean of immediate samples	Standard error of mean	Time of later samples	Mean of later samples	Standard error of mean
10	0.0115	±.0022	24 hrs.	0.0085	±.0014
10	0.0100	±.0021	48 hrs.	0.0078	±.0024
4	0.0075	±.0042	72 hrs.	0.0100	±.0021

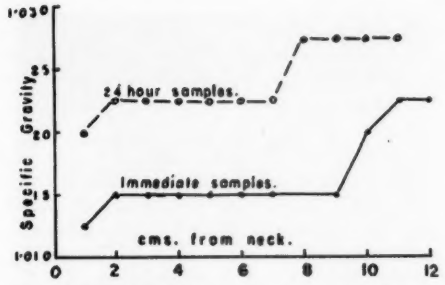

Fig. 6. Shift in specific gravity in a beef gall bladder after hanging 24 hours.

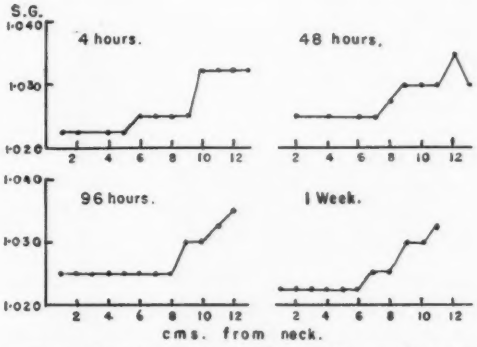

Fig. 7. Persistence of gradient of specific gravity in bile dripped into a graduated cylinder.

specific gravity samples, that the concentration of bile in the gall bladder is far from homogeneous.

In addition to the specific gravity determinations made as soon as possible after death, determinations were made 24 hours later on the same bladders in 10 cases, 48 hours later in 10 other cases, and 72 hours later in 4 cases. The means with their standard errors are given in Table II.

Except for the difference between the 24 hour and immediate samples, where there is a slightly significant change, there is no evidence of diffusion having significantly decreased the inhomogeneity in the contents of these gall bladders. It is to be noted, however, that though the gradient had not changed, in most cases all the specific gravities were higher in the 24 hour samples than in the corresponding immediate samples (Fig. 6). This is probably due to evaporation and possibly to the absorption of water by the wall of the bladders in the period. The character of the stratification remained the same in spite of evaporation and the removal of the samples. In the case in which the contents of a gall bladder were allowed to drip slowly into a tall graduate, the gradient was found to persist even after 1 week (Fig. 7).

Diffusion between the strata is certainly remarkably slow, so that once present, the stratification persists. To determine whether or not diffusion would be equally slow in a similar system with comparable viscosity and specific gravity, an artificial stratification was made of 18 per cent glycerine in water, under distilled water. The results are shown in Figure 8. The diffusion, though slow, is definitely faster than in the case of stratified bile, so that in the latter some other physicochemical factor than viscosity and specific gravity must play a part. The strongest evidence that mixing of the strata hardly occurs, even with mechanical agitation, is that stratification was found in the gall bladders of these cattle, though in the process of killing and removal of the gall bladders there had been quite violent changes of position.

Human gall bladders. A short series of experiments on human gall bladders obtained at operation is included here. A longer series on human material is being accumulated by one of us and will be presented later elsewhere.

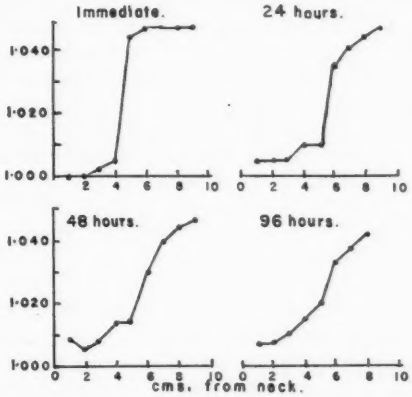

Fig. 8. Change of gradient in specific gravity due to diffusion in a layered sample of distilled water over an 18 per cent glycerine solution.

(Operative procedures were not carried out by the authors.)

In each case an attempt was made to remove samples of bile from the bladder *in situ*, that is before it had been disturbed by the manipulations occasioned by its removal. Following removal, samples of bile were drawn from the bladder, suspended with the fundus down, at intervals of 1 centimeter. On these two sets of samples, specific gravity and other determinations were made. Of the series of 5 bladders, on 3 both sets of samples were obtained, on 1 it was possible to obtain samples only after removal, and on 1 bladder samples were obtained only before removal. In 1 case it was possible to obtain complete roentgenological investigation, i.e. pictures of the bladder preoperatively, as well as postoperatively, in both the supine and upright positions.

Figure 9 shows the layer of small floating stones visible when one of the patients was in the erect position. The stones were also visible, again floating in a horizontal line, when the patient was in the supine position. Roentgenological examination revealed that a good degree of functional contractility and of concentration by the gall bladder was present. Figure 10 shows the results of analysis of samples from this bladder before and after operation. The dotted line represents the level at which the stones floated. There were 19 of these all of specific gravities between 1.040 and 1.0425, so that they were evidently floating in bile of their own specific gravity. This case illustrates the existence of marked stratification of bile in a human gall bladder and the fact that floating stones occur near the region in which the specific gravity changes abruptly. Two other cases of the 5 showed marked differences of specific gravity from top to bottom, and evidence of stratification The series of values of specific gravity in samples from top to bottom ran, in the 2 cases:

1.020, 1.020, 1.025, 1.0375, 1.0375, 1.0375 in one case and 1.015, 1.015, 1.015, 1.015, 1.0175, 1.0175, 1.0275 in the other.

In these cases, the stones that were present were not floating but at the bottom. This brief series of human cases serves to show that the phenomena of stratification, suggested by the radiological evidence of Bernstein in normal as well as diseased humans, can be found by other methods, in humans as well as in cattle and cats.

DISCUSSION OF RESULTS

A series of experiments has been described in which the bile of the gall bladders of cats, cattle, and human beings has been investigated for evidence for or against the presence of strata as observed roentgenologically. The results show that the bile of many normal gall bladders is not of a homogeneous composition throughout and that the stratification is remarkably persistent in spite of diffusion. Furthermore, the presence of strata has been demonstrated in a sufficiently large number of these bladders to justify the conclusion that stratification occurs as a normal physiological phenomenon in the functioning gall bladder.

The fact of persistent inhomogeneity of the contents of a gall bladder in the normal physiology of these animals, as well as in cholelithiasis, has an important bearing on the interpretation of previous researches. For example, when small samples have been withdrawn from gall bladders at successive times to indicate the progress of concentration within the bladder, the question must be raised whether such samples were representative of the contents as a whole, and so could give reliable information. Some of the reports of astonishingly rapid concentration may have been due to the withdrawal first of more dilute samples from high in the bladder and later of samples of greater concentration from a stratum below.

A simple explanation of the formation of strata of bile in the gall bladder may be suggested. Let us suppose that after filling with dilute hepatic bile, the gall bladder has considerably concentrated this before a contraction occurs. Unless this contraction is complete, expelling all of the contents, there will be a residue of concentrated bile. Relaxation of the gall bladder will draw in, on top of this, a more dilute hepatic bile. If, as has been demonstrated, the two biles do not readily mix, there will then be two distinct layers of bile in the bladder. A second partial contraction and relaxation might introduce a third

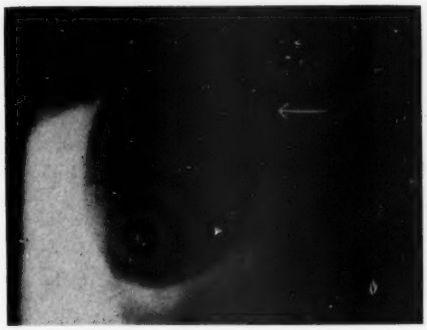

Fig. 9. Roentgenogram of patient with floating gallstones, taken in the erect position.

layer, and so on. Thus the presence of stratification would be primarily due to the incompleteness of contraction of a gall bladder which is still able to concentrate.

It has been demonstrated that once established, such stratification is remarkably persistent and resists mixing by mechanical agitation. The roentgenological evidence and evidence in humans here reported strongly suggest that the floating gallstones are associated with interfaces between two biles of different concentration. This suggests that the precipitation of cholesterol may be favored at such persistent interfaces by a physicochemical mechanism.

An observation on the population of multiple cholesterol stones in a human case is pertinent, which can be explained by the picture

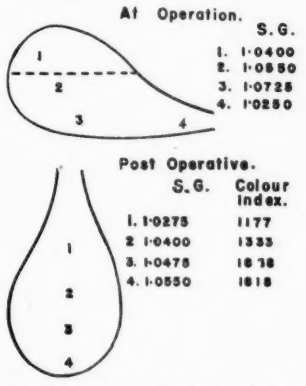

Fig. 10. Results on samples of bile taken from human gall bladder shown in Figure 9.

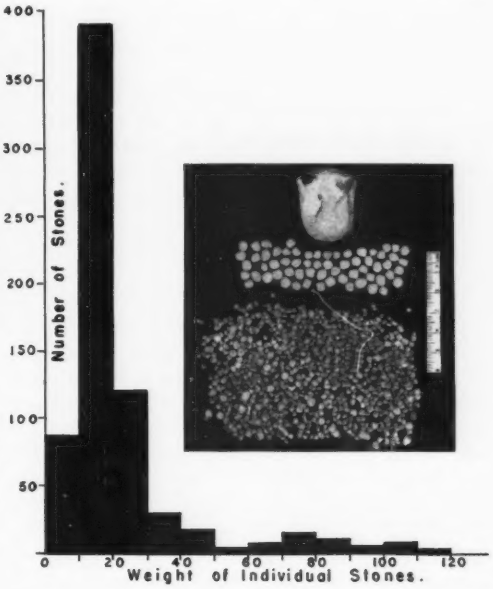

Fig. 11. Population of multiple stones in a human gall bladder, showing distinct "families."

of events just described but is difficult on other theories. This gall bladder was full of a very large number of stones of greatly different sizes, as well as one large calculus filling the fundus. On inspection, the stones could be segregated into what appeared to be three distinct groups (Fig. 11). All were weighed and a statistical population study made. The histogram (Fig. 11) shows that there are, as well as the large calculus, at least two statistically distinct "families" of gallstones (corresponding to the maxima in the graph), indicating that there must have been several distinct new beginnings of such families. A new partial contraction and drawing in of a new layer of hepatic bile above the concentrated layers might well be the starting point of each new family of stones.

Theories of cholelithiasis can be grouped under two headings. First, there is the "metabolic theory" in which it is thought that the bile secreted by the liver into the gall bladder is not of normal composition and that this somehow leads to precipitation of calculi. The second theory is that of "infection," in which

infection of the gall bladder wall by altering the absorption of different constituents of the bile is thought to bring about the precipitation. The work here reported suggests that a third factor cannot be neglected. Mere inability of the gall bladder to contract completely, leading to infrequent or incomplete emptying of the contents, may itself favor the precipitation of cholesterol stones because of persistent stratification of the bile.

CONCLUSIONS

It is concluded from these experiments that in cats, cattle, and in humans the contents of the gall bladder are far from homogeneous as regards specific gravity, concentration of bile pigments and hydrogen ion concentration, and that this is a physiological rather than a pathological phenomenon. The inhomogeneity is often so abrupt as to suggest that distinct "strata" of bile of different degrees of concentration coexist. The observations also show that when such stratification exists, it is remarkably persistent and resists the process of diffusion and quite violent mechanical agitation.

The formation of such strata is readily explained in terms of incomplete emptying of a gall bladder which is able to concentrate the bile. The consequences of long persistent stratification have not been demonstrated, but there is suggestive evidence, in cases of floating multiple stones, that it may favor the precipitation of cholesterol stones.

SUMMARY

1. Samples of bile withdrawn at different levels in dependent gall bladders of cats, cattle, and of some humans have been examined as to their specific gravity, concentration of pigments, viscosity, and hydrogen ion concentration.

2. A lack of homogeneity from top to bottom is the rule rather than the exception. In 65 gall bladders of normal cattle, 60 per cent showed an increase in specific gravity, from top to bottom, of .005 to .023 unit. Changes in hydrogen ion concentration and in color index closely paralleled the changes in specific gravity. Changes in viscosity were not well correlated.

3. The changes were often so abrupt as to show the existence of two or more distinct strata.

4. Neither the process of diffusion for as long as a week nor considerable mechanical agitation was able to mix these strata.

5. In 2 of the 5 human cases, cholesterol stones were floating at the level of the interface between two strata.

6. A theory of the formation of such strata in terms of incomplete emptying of a gall bladder, able to concentrate, is suggested.

7. The possibility is discussed that persistent stratification of bile may favor the precipitation of cholesterol stones.

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VASCULAR CHANGES OF THE SKIN IN PREGNANCY

Vascular Spiders and Palmar Erythema

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ALTHOUGH American textbooks on obstetrics do not mention them, there are scattered references in medical writings to vascular spiders and palmar erythema as banal complications of pregnancy which tend to clear up following delivery (4, 6, 7, 8, 11, 12, 13, 14, 15, 16, 17, 18, 23, 24, 29, 30, 32). The general subject of vascular spiders and palmar erythema has been the theme of extensive reviews; and there has been a revived interest in these phenomena recently with many contributions from internists and dermatologists. No systematic study of these vascular lesions and their natural history in pregnancy has been made although there are reports of changes in capillaries (20). We therefore undertook a comprehensive investigation of the problem in the clinics and on the wards of the obstetrical service of the Cincinnati General Hospital. In addition we have collected from the literature all related reports we have been able to find. The significance of these vascular changes in the skin is not known but clinical relationships suggest that there is some connection with endocrine changes. These are under investigation. It is hoped that more attention will be given these phenomena by specialists in the fields of obstetrics, endocrinology, and gynecology. The purpose of this paper is to report the results of the clinical study and a review of the literature. The completed analysis of all possible correlations among the observations made will be reported later.

DESCRIPTION OF THE VASCULAR SPIDER AND PALMAR ERYTHEMA

The vascular spider has been called by many names; it has been designated nevus, angioma, and telangiectasis. The type occurring in persons with chronic liver disease has been described in detail elsewhere (6). Three features characterize the usual variety, a *body*, *legs*, and surrounding *erythema*. A central point or eminence constitutes the body of the spider, and in small or beginning lesions this may be the only abnormality. In large ones it may project one or more millimeters above the level of the surrounding skin surface, and when of sufficient size its pulsations may be felt. Branching legs or radicles come away from the body and decrease in size as the periphery is reached. There may be some irregularity of the legs as they dip out of sight and reappear further away from the center. The entire area encompassed by the legs is redder than the adjacent skin and in some instances the erythema may occur with few or no visible radicles. The skin may reveal other changes consisting chiefly of scattered vascular strands which have a resemblance to the silk threads in American paper money. In studying the earliest visible changes in the skin during pregnancy we have seen several instances of a very pale area in the skin later becoming the site of a vascular spider. After one or more weeks a red spot of pin head size appears in the center of the pale area, and this gives rise to the anemic halo (Fig. 1) which has been described (23) and pictured before (12). Not all of these pale spots subsequently develop vascular changes; some gradually disappear. The temperature over a vascular spider is higher than that of the surrounding skin because of the local increase in arterial blood. A fiery red color is characteristic and the lesion does not appear in infra-red photographs (5). Blood flows from the body toward the periphery as may be seen in the refilling of a spider following its obliteration by pressure, or by gently pressing a glass slide over the area. There is a curious predilection for distribution

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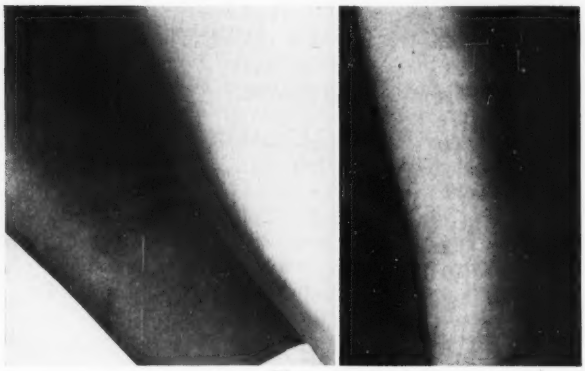

Fig. 1.

Fig. 1. The anemic halo. This is the earliest stage of the vascular spider where a punctate red spot is found occupying the center of a small area paler than adjoining skin.

Fig. 2. Typical large vascular spiders, one of which has been covered with oil to reveal the vessels radiating from the center. In those not covered with oil the erythema surrounding the central punctum is prominent.

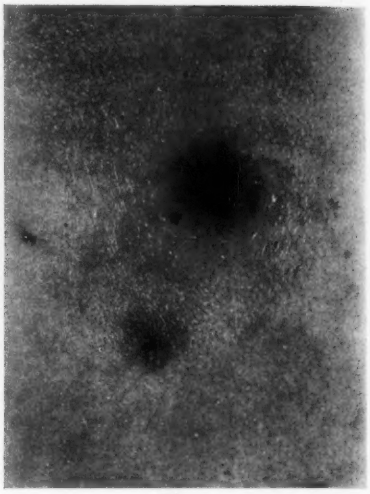

Fig. 2.

over the upper parts of the body with the face, neck, upper chest, and arms frequently affected. It should be emphasized that as the study progressed with repeated scrutiny and concentration we have detected smaller and smaller lesions. Indeed, in certain persons with lightly pigmented skin which had a conspicuous pattern of vascular marking we noted spiders appear at the level of barely perceptible visibility in the pale regions. Thus a single small red spot appeared to be surrounded by an anemic halo. Later the body grew larger, legs sprouted outward and grew in a centrifugal direction, branching when they reached sufficient size. We have recorded as spiders in our data only such lesions as we were able to record by ordinary black and white photography. Various types of lesions are illustrated in Figures 1 to 6.

Fig. 3. Characteristic vascular spider on the dorsum of the hand.

We have no observations on the microscopic characters of the vascular spider or palmar erythema of pregnancy. Histological details of the spider of chronic hepatic disease have been published elsewhere (6).

Palmar erythema may occur in two distinct forms in women during pregnancy. The first variety is similar to the "liver palms" of chronic hepatic disease. It begins as a diffuse redness most prominent in the proximal part of the hypothenar eminence. Cyanotic spots may appear in the red areas. In more advanced stages the thenar eminence is involved also and a more extensive area of the hypothenar eminence becomes bright red. Next the parts of the palm between the metacarpophalangeal joints develop red spots and the palmar pads of the finger tips become red. Later the base of the nails may be affected. The red areas are sharply separated from adjoining skin of normal color. The other variety consists of a diffuse mottled erythema involving the entire palmar surface with a speckling of pale areas a millimeter or more in diameter. This is an exaggeration of the nor-

Fig. 4.

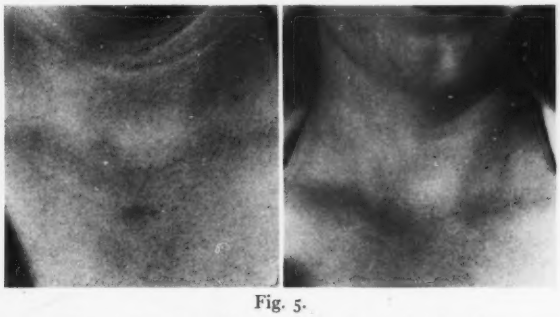

Fig. 5.

Fig. 4. Vascular spider on bridge of nose showing elevation of body above the level of surrounding skin. Pulsation is felt readily in this type of lesion.

Fig. 5. Vascular spider appearing below jugular notch during pregnancy and follow-up photograph demonstrating that it has disappeared by the seventh week following delivery.

mal mottling of the palm. At times there is a patchy cyanosis of parts of the palm so that there is an irregular display of red, white and blue. There is a tendency for the vascular markings of the palm to show some variation, part of which is spontaneous and part of which may be induced by elevating or depressing the hand. In some instances the type of erythema has changed during the course of observation, and the localized type has become the diffuse type or vice versa. There is a trend for redness to increase in intensity as pregnancy runs its course. This may be pronounced early after the first appearance of redness, or may be gradual throughout gestation. These vascular changes of the hand have no regular relation to edema of the hands. A number of women studied before palmar erythema became apparent had cold sweating hands and an increase in the vascular markings of the arms with reticulated areas of cyanosis surrounding pale islands of skin similar to the pattern which may become fixed in erythema *ab igne*. The types of palmar erythema are demonstrated in Figures 7 to 9.

REVIEW OF THE LITERATURE: VASCULAR SPIDERS

In an earlier paper (6) one of us reviewed some of the casual and detailed reports of vascular spiders in pregnant women, and pointed out the curious complete absence of comment on these common vascular changes in American textbooks of obstetrics.

So far as we have been able to determine, the first observation of spiders appearing during the course of pregnancy was recorded by Corbett in the *British Journal of Dermatology* in 1914 (11). He merely stated that he had seen spider angiomas appear in the skin during pregnancy and disappear entirely after delivery. The next note on cutaneous spiders in pregnancy was recorded by Zeisler (32). He suggested the possibility of syphilis as a causative agent. Konrad (17) gave a more detailed description in 1925, calling attention to the

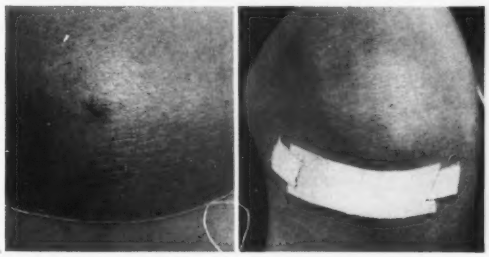

Fig. 6. Vascular spider on the knee, a very rare location, and subsequent picture revealing its disappearance following delivery.

Fig. 7. Palmar erythema. On the left is the variety which is most marked on the hypothenar eminence with involvement of the thenar eminence, the palm between the pads near the metacarpophalangeal junction, and the finger tips. On the right the palm is diffusely involved with a mottled erythema, cyanosis, and pallor which is an exaggeration of the mottled pattern seen in the normal hand.

appearance of telangiectases on the face, neck, and arms during the second month of pregnancy. This was the first emphasis on the distribution over the upper parts of the body so characteristic of the acquired cutaneous spider of pregnancy as well as that of hepatic disease. The abrupt fading or disappearance of these marks in the postpartum period was observed. A similar finding was reported in a woman who had a pituitary tumor (1), and the possibility was considered that an endocrine disorder might be responsible for the skin lesion. Two examples of spiders in pregnancy were encountered by Urbach (26), who described them in detail. They vanished shortly after delivery. Gougerot and Meyer (16) suggested a possible familial tendency. They observed the appearance of typical spider-like angiomas during the fifth month of pregnancy in four consecutive gestations, in a woman whose two sisters had also acquired spiders during pregnancy. Because of syphilis in the family, they believed the lesions to be stigmas of hereditary syphilis. Distribution on the neck, arms, and hands was noted. There were no mucosal lesions and no tendency to bleeding.

Another report (23) described a case in which spiders were not present during the first and second pregnancies but in the third month of the next pregnancy appeared on the neck, chest, and arms. The paper included a description of spiders of several varieties and sizes, with the larger ones typical in shape, having an elevated central boss and a peripheral anemic halo. The authors believed the distribution was related to the cutaneous nerves derived from the brachial plexus. In a report by Madden on generalized angiomatosis (19) 2 cases of vascular spiders acquired during pregnancy were included. In one, a 30 year old white woman, they appeared during the third month, increased in number up to the seventh month and all disappeared about 2 months after the second pregnancy was terminated. Similar smaller lesions had appeared during the first pregnancy. Another patient acquired similar vascular spiders in the fifth month of pregnancy. Mitchell (21) referred to 3 similar cases.

Forman (15) described a case in which the woman acquired spiders early in the second month of 11 consecutive pregnancies, each of which ended with delivery of a stillborn fetus before term. The spiders faded rapidly within a week after labor. He believed that an endocrine disturbance was responsible. In addition the coming and going of cutaneous spiders concurrently with the waxing and waning of symptoms in a patient with peptic ulcer was noted. Vignes, Hanoun, and Vial (29) have reviewed some of the European literature on spiders in women during pregnancy and have recorded their familiarity with this lesion. Davis (12) has contributed a learned discussion of subcutaneous hemangioendotheliomas associated with pregnancy in which he discusses the rare malignant variety and includes a number of excellent photographs of typical vascular spiders. He collected a series of 11 such cases during a 2 year period from various antenatal clinics. The description given of a type characterized by a "pigmented, warty growth projecting under the superficial layers of the skin" classes it as one of the pigmented warts discussed by Brickner (9, 10). The suspected relationship of this type of lesion to the much commoner vascular spider of pregnancy has been discussed (6).

Smith (24) has recorded observations on spider nevi appearing during the last month of the second pregnancy in a 26 year old woman.

Fig. 8. Photograph of the hand during and after the occurrence of the sharply localized variety of the palmar erythema of pregnancy.

During a third pregnancy they appeared again on the back and upper chest during the fifth month. Some idea of the difficulty of tracking down medical reports of this phenomenon can be seen in the title of Smith's note—"The Treatment of Hereditary Telangiectasia."

Walsh and Becker (30) in their monograph on erythema palmare and naevus-araneus-like telangiectases gave full description of 6 cases in which vascular spiders developed during pregnancy (in 4, palmar erythema was also present). In some of the patients spiders had been present before pregnancy. Their advent occurred anywhere from the third to seventh month of pregnancy. Spiders tended to parallel the palmar erythema in the time of appearance and disappearance, but there were some exceptions. These authors discussed the number, size, configuration and distribution of the vascular spiders. For the first time arterial pulsation was described in the spider of pregnancy. Their investigation included inspection with the capillary microscope and histologic study. A low-power view of one of their biopsy specimens gives a clear idea of the two types of vessels encountered, (1) the thick coiled stem artery in the subcutis branching directly into (2) "veins" of comparable size. This they termed an arteriovenous anastomosis, but did not note that it is not a true arteriovenous anastomosis, but has a multitude of "veins" branching from a central artery, and these "veins" distribute blood into

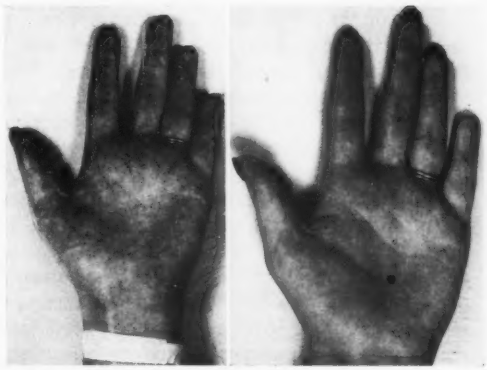

Fig. 9. The hand during and after the occurrence of the diffuse mottled palmar erythema of pregnancy.

a capillary bed before it is conveyed away in true veins. They did not find any evidence of hereditary tendency except in the cases presenting palmar erythema, nor did they see any indication that the spiders had followed "minor trauma" such as mosquito bites, pinpricks, and the like. There was no incrimination of syphilis or hepatic disease. They thought the most probable cause to be some endocrine disturbance. Newman (22) believed the cause was an increase in blood volume plus the effects of the hormone progesterone.

Bean (6) reported observations in 41 women who acquired vascular spiders during pregnancy. In many instances they were observed to appear from the second to the fifth month of

pregnancy. Usually they disappeared at, or shortly after, the time of delivery. There was no indication that hepatic disease was responsible for the vascular spiders in the women observed. Data from pregnant women (27, 28) might support the suggestion that quantitative changes in circulating estrogens are responsible for the appearance of acquired vascular spiders in pregnancy (6) and hepatic diseases.

REVIEW OF THE LITERATURE: PALMAR ERYTHEMA

It is likely that earlier references to palmar erythema acquired during pregnancy exist but the first notice of it that we have found was that by Feldman in 1939 (13, 14). In a very brief comment he discussed a woman in whom redness of the palms appeared during her second, third, and fourth pregnancies and disappeared when pregnancy was terminated. He speculated about a possible relationship to increased blood volume and the hormone progesterone. Walsh and Becker (30) have contributed the classic paper in this field and were the first to record the concurrent appearance of vascular spiders and palmar erythema in pregnancy with their subsequent clearing after delivery. Much of the early literature on palmar erythema was reviewed by these authors.

In a brief note (3) one of us suggested that vascular spiders and palmar erythema observed in pregnancy, chronic hepatic disease, and nutritional deficiency disorders might be caused by estrogenic hormones, and presented preliminary studies which indicated that such changes in blood vessels of the skin might be induced by administering estrogens to susceptible persons. In the first paper exclusively devoted to the subject of erythema of the palms in pregnancy, Lofgren (18) described in detail 3 cases he had investigated. He presented striking photographs of the return to normal which had occurred by the fourth postpartum month in a woman with the palmar erythema of pregnancy. He made the suggestion independently that estrogenic substances might be responsible for their appearance. To test his hypothesis he administered estradiol benzoate to one of the women 4½ months after delivery. There was definite increase in the palmar redness, but it did not reach the intensity of the erythema present during pregnancy.

A review of the subject of palmar erythema and cutaneous vascular spiders (4) included the suggestion but no further evidence that these changes in the skin were related to high levels of circulating estrogens. No discussion of the problem in pregnancy was included. In an extensive survey of the cutaneous arterial spider (6) it was mentioned that the anatomical substrate of palmar erythema might be related to the arteriovenous glomus bodies so profusely distributed in the palmar skin. In addition to hepatic disease and normal pregnancy, palmar erythema is common in pulmonary tuberculosis (2, 25) and it was suggested that clubbing of the fingers may be related to the associated increase in blood flow (4).

These few references are all we have been able to find in searching recent medical writings on the subject. Doubtless there are other reports. One of the main reasons for undertaking this study was the lack of any systematic information on the incidence, course, and probable significance of vascular spiders and palmar erythema which occur during pregnancy.

PROCEDURES

The present study was set up to learn what we could of the natural history of the vascular spider and palmar erythema acquired during pregnancy. Thanks to the co-operation of members of the obstetrical service we were permitted to examine each patient seen on every visit to the prenatal clinic, during hospitalization for delivery and again at the postpartum visit 6 weeks after discharge following the 4 to 10 days of hospitalization for delivery. All initial examinations were made by the senior author and subsequent ones were made by various members of the group in addition. Observations were begun in July, 1946, but it was not until October, 1946, that every woman was examined on each clinic visit. At that time a system of examination and record keeping was put into effect. Because there was neither adequate time nor personnel our inspection was limited to the hands, lower and upper arms, face, neck and upper chest. Con-

ditions of lighting were kept constant. An artificial blue light was used and all patients were examined while standing before the light. A record was kept of the presence or absence of vascular spiders and their location and number, if present. Palmar erythema was recorded, if present, and whether of the diffuse or sharply localized form. A notation was made of the depth of skin color in both white and negro patients. A very large number of photographs was taken, and in some cases a series of them was made throughout pregnancy, in the hospital shortly after delivery and again at the final postpartum visit. In patients who had either type of vascular change in the skin an effort was made to ascertain its time of appearance, but this information was not very reliable except that some patients were aware of vascular spiders or palmar erythema antedating pregnancy. Others had never noticed either. In some instances we collected 24 hour specimens of urine for hormone assay but the results are not adequate for detailed analysis. In a few patients liver function studies were done.

Our subjects included all women examined in the prenatal clinic who were in attendance in October, 1946, and all new clinic patients who came in through October 23, 1947.

Our discussion where possible deals with the largest number of cases fully studied. In most instances data are derived from all pertinent records, but in some of the figures only those with complete records were included. Records were designed so that the information could be transferred to International Business Machine punch cards to facilitate processing. Charts of distribution of vascular spiders were kept to follow individual lesions. Degree and type of palmar erythema were noted.

In order to make extensive correlations with other data concerning the patient and her offspring we obtained information on age, color, parity; on sex, weight, viability and normality of offspring; on complications related to toxemia and eclampsia; on lactation; and season of the year. The date of the last menstrual period was recorded in order to learn the time in pregnancy when the skin lesions appeared or the duration of pregnancy at the time of the first visit if lesions were already manifest. The date of delivery was recorded and in the final analysis the time of appearance of vascular changes was based on recalculation from date of delivery in all pregnancies which went to term. Some of the possible correlations have been made but many await future study.

The total number seen in the clinic was 1,243. There were 484 white and 759 negro women. Records have been fully analyzed on 392 women who were seen during hospitalization and at the routine postpartum visit. An additional 537 were seen during the week after delivery but had not returned for follow-up in spite of our special efforts to make a final examination. The remainder were under observation when we began compiling this paper.

OBSERVATIONS: VASCULAR SPIDERS

Vascular spiders were found in 321 or 66.6 per cent of the 484 white women observed, and in 87 or 11.4 per cent of the 759 negro women at some time during pregnancy.[1] Since women presented themselves at varying stages of pregnancy for their first clinic visit our figures on incidence of spiders throughout pregnancy are not derived from large numbers, there being relatively few women seen during the second and third months of pregnancy while the totals were very high by the last month. In Figures 10 and 11 we have calculated the percentage of all women seen in any month of pregnancy who had vascular spiders at that time. There were relatively few subjects seen in the early months of pregnancy. In Figure 10 it is seen that 14 per cent of white women had vascular spiders by the second month of pregnancy. For the next 3 months there was a general tendency for the proportion having spiders to increase rapidly. Following this there was a slow but steady increase of positive cases up to the time of delivery. By the ninth month of pregnancy 66 per cent of all white women under observation had vascular spiders. We do not have all the control observations desirable on incidence of vascular spi-

[1]The discrepancies between the numbers in the text and those in Figures 10, 11, 14, and 15 have resulted from our using data only from completely observed cases in the charts—women seen prenatally, at and after delivery, and at the routine postnatal follow-up. Numbers in the text are derived from all records with relevant information, even if follow-up is lacking. No difference has been more than 5 per cent.

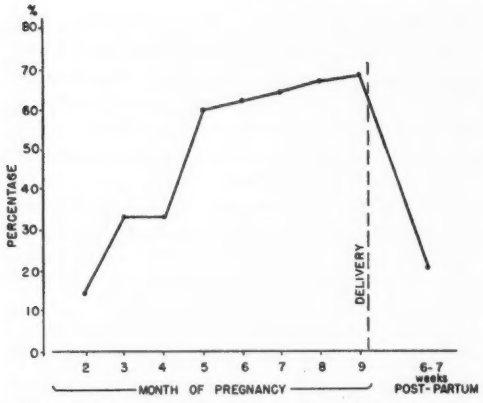

Fig. 10. Percentage of white women with vascular spiders during and after pregnancy.

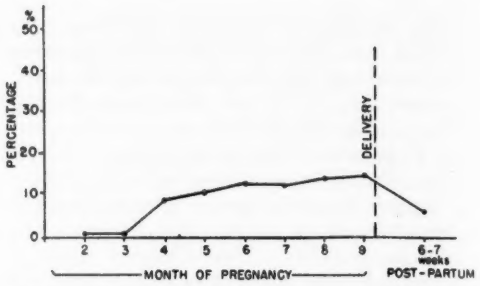

Fig. 11. Percentage of negro women with vascular spiders during and after pregnancy.

ders in unmarried, childless, or parous women of various ages. In order to get some idea of their incidence in a representative group of women we observed 58 nonpregnant white women who had one or more children and found typical vascular spiders in 12 per cent. While the number of women without a history of pregnancy might well supply a lower figure, the percentage of white women with spiders during pregnancy is significantly and markedly higher than the control group of nonpregnant women who had borne children. Other control observations are given in Table I.

Nine white women had vascular spiders which they were certain had existed before the first pregnancy.

Findings in negro women are different, chiefly in the much lower incidence of vascular spiders in members of this race. In Figure 11 we find that no spiders were observed prior to the fourth month, by which time they had appeared in 8 per cent of all subjects seen during this month. The incidence rose slowly thereafter until a peak was reached in the ninth month when 14.2 per cent were found to have spiders.

This notable discrepancy between incidence in white and negro women highlights an aspect of the study in which we have correlated the depth of skin pigmentation with the finding of vascular spiders among both white and negro women. An estimate of degree of pigmentation of the skin was made on each person and recorded as light, medium, and dark. White women with red hair were recorded in a separate category. This was checked at each clinic visit without access to previous estimate of pigment by the observer. While this is at best only a semiquantitative evaluation there was surprising consistency in the routine observations by each member of the study group, and good consistency between different observers. In Figure 12 we have charted the percentage of women with different depths of skin pigment in whom we observed vascular spiders. There was a consistent tendency for them to be found more often in those with skin of lighter color. This may indicate merely the obvious fact that vessels in the skin can be seen more readily in persons with light skin but the additional possibility exists that there is a greater tendency for such vascular lesions to develop in women with light skin. There was a similar trend among negro women whose depth of skin pigment was recorded as light, medium, or dark.

In Figures 10 and 11 the highest incidence of vascular spiders in white and negro women during the last month of pregnancy is compared with their incidence at the regular postpartum follow-up. In white women the percentage fell from 69 to 20. In negroes the corresponding change was from 14 to 5 per cent. Thus about three-fourths of the women who had vascular spiders in the ninth month of pregnancy had lost them by the seventh week after delivery. In Figure 13 we have given in detail the rate at which vascular spiders and palmar erythema were lost during the last month of pregnancy and during the puer-

TABLE I.—INCIDENCE OF VASCULAR SPIDERS AND PALMAR ERYTHEMA IN CONTROL GROUPS

	Number	Negative %	Spiders %	Palmar erythema %
Normal white women	58	86.2	12.0*	5.1*
Normal negro women	51	96.0	0.0	4.0
Normal white soldiers	295	85.1	14.9	0.0
Normal negro soldiers	42	100.0	0.0	0.0
Laennec's cirrhosis	151	25.0	75.0	42.0†

*Spiders and palmar erythema occurred together in 3.4 per cent.
†Date not complete.

perium. Data are derived from all subjects with observations, regardless of follow-up. A few women suddenly lost vascular spiders, or they decreased in size during the month before delivery, but this was uncommon. The period of most rapid loss of spiders was during the week immediately following delivery. The loss thereafter was more gradual up to the time of our final observation. In the few women whom we have seen up to a year after delivery there has been a further decrease in size and number of lesions unless another pregnancy intervened. In Figures 10 and 11 the data for disappearance refer to women who had lost all vascular spiders. In those still positive at the postpartum check-up many had lost some but not all of the lesions, and in others they had decreased in size so the quantitative aspects of the changes were even more dramatic than is suggested from the figures. There was a tendency for lesions which appeared late in pregnancy to fade early, and those which appeared early to disappear some-

TABLE II.—DISTRIBUTION OF SPIDERS IN WHITE AND NEGRO WOMEN

Area	White (529 lesions) %	Negro (105 lesions) %
Face	11	12
Neck and anterior chest	14	5
Arm, upper anterior	7	5
Arm, upper posterior	8	3
Arm, lower anterior	14	9
Arm, lower posterior	21	17
Palm	7	20
Dorsum of hand	18	29
Others	(knee 1 case)	

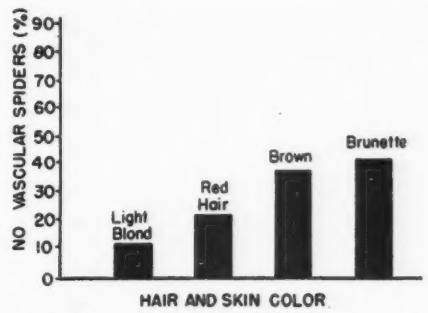

Fig. 12. Percentage of white women with different hair and skin color having *no* vascular spiders.

what later. This is partly related to size of individual spiders, the larger ones usually taking longer to vanish completely. Without charts marking the area of each lesion, and photographic records, usually it was impossible to identify precisely the area where a spider had been. At times a small freckle marked the spot, and at times the skin was slightly atrophic, but these were exceptional findings. In 3 instances we noted spiders after delivery which were not recorded before. We believe this represents an earlier oversight rather than the actual development of new lesions during the puerperium.

In Table II we have compared the location of vascular spiders in white and negro women. There are notable differences. In negroes the hand was the site of about half the spiders, whereas in white women it was the site of only a quarter of the lesions. The difference was even more striking where the palm was considered, lesions being almost three times as common on the palm in negro women as in white women. The other findings are given in the table. Aside from differences in pigmentation, we have no ready explanation for these contrasts.

OBSERVATIONS: PALMAR ERYTHEMA

Palmar erythema was observed in a total of 300, or 62.5 per cent, of the white women and 263, or 35 per cent, of the negro women in this study. Figures 14 and 15 give the incidence throughout pregnancy and by the time of the postpartum follow-up. The trend of appearance of palmar erythema in Figure 14 was

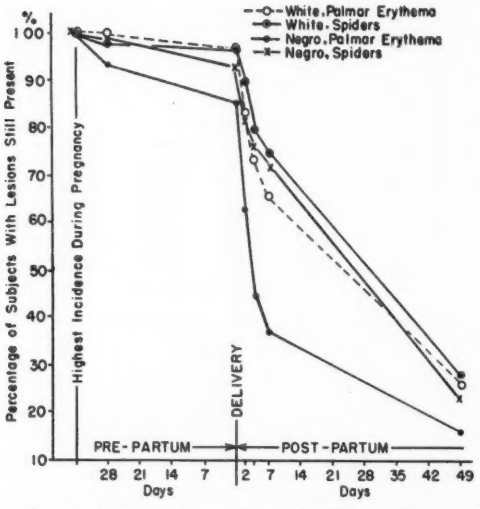

Fig. 13. Rate of disappearance of vascular spiders and palmar erythema expressed as per cent. Subjects were called positive when either type of palmar erythema was noted, or one or more spiders. They were classed as negative when all vascular spiders or the palmar erythema had disappeared.

considerably different from that for vascular spiders in Figure 10. While only 14 per cent of the white women seen in the second month of pregnancy had vascular spiders, palmar erythema was present in 33 per cent at that time. From the second through the ninth month there was a gradual rise. The dip in the curve from the third to the fourth month does not mean that some women lost their palmar

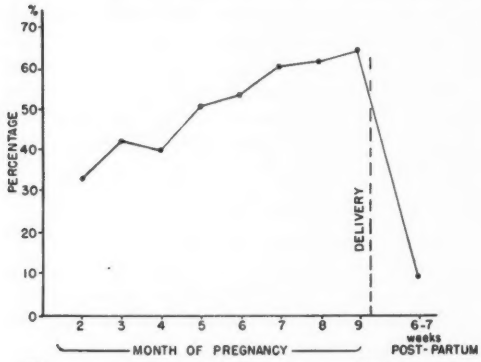

Fig. 14. Percentage of white women exhibiting palmar erythema during the course of pregnancy and after delivery.

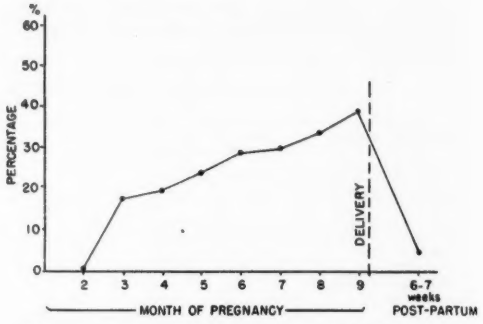

Fig. 15. Percentage of negro women exhibiting palmar erythema during the course of pregnancy and after delivery.

erythema during this time but that it was less common in the women making their first clinic visit during the fourth month. By the time of the regular postpartum visit palmar erythema had faded in all but 9 per cent of the women. This compares with 20 per cent who retained vascular spiders at this time. Three white women had palmar erythema before the onset of the first pregnancy and in two it existed in other members of their family.

In Figure 15 the curve for incidence of palmar erythema in negro women is given. This may be compared with a similar curve for vascular spiders in Figure 11. While no instance was found in the second month, palmar erythema had appeared in 17 per cent by the third month, and there was a slow but steady rise to a peak of 39 per cent by the ninth month. This had fallen to 4 per cent by the postpartum follow-up. Palmar erythema was almost three times as common as vascular spiders in negro women while there was only a slight difference in the incidence of vascular spiders and palmar erythema in white women. The most probable cause is the variation in skin pigment which is much less deep in the palms than in other areas of skin of negro women.

In Figure 16 the time of appearance has been compared with the time of fading of palmar erythema. There is an indication that the lesion appearing late fades early and vice versa. In 10 per cent the lesions disappeared before or during the last week of pregnancy, a larger proportion than in the case of vascular

TIME OF DISAPPEARANCE	3	4	5	6	7	8	9	TOTAL
STILL PRESENT			1		1		1	3%
7 WEEKS POST-PARTUM	1	2	1	1	3	2	7	17%
1-7 DAYS POST-PARTUM		2	3	8	6	8	15	42%
24 HOURS AFTER DELIVERY			1	3	5	5	14	28%
LAST WEEK OF PREGNANCY				2	3	4	1	10%

MONTH OF ONSET DURING PREGNANCY

Fig. 16. Comparison of the month of appearance and the time of disappearance of palmar erythema.

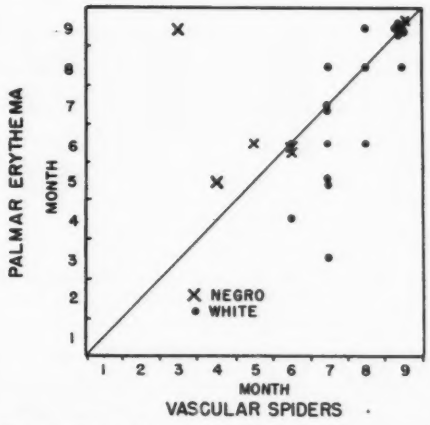

Fig. 17. Comparison of known month of appearance of palmar erythema and vascular spiders. Each point or x represents 1 case.

spiders. Palmar erythema tended to fade more rapidly in negro than in white women (Fig. 13). We believe that the change in the vessels in the palm is more labile and has a considerable functional element. The distribution and intensity of the redness change from time to time. There is some spontaneous variation in the combinations of mottled erythema, cyanosis, and pallor in many instances. There is a more abrupt onset and fading is complete in more women at the time of follow-up.

We have found no explanation for the fact that either palmar erythema or vascular spiders may occur alone, or in association with the other. Palmar erythema was observed in 67 per cent of the white women who had vascular spiders. Vascular spiders were observed in 71 per cent of the white women who exhibited palmar erythema. Thus if either type of vascular change was found the other was about twice as likely to be present as to be absent. This suggests but does not prove that there may be a common cause. In Figure 17 we have plotted the known month of appearance of vascular spiders and of palmar erythema. There is a tendency for them to occur near the same time but there are notable exceptions. Further data are needed to determine whether the tendency for palmar erythema to appear before spiders in negro women and the reverse in white women is substantiated. Their parallel course of increase in intensity throughout gestation, and similar rapid decrease or disappearance is further support for this idea. One may suggest that the sites affected, i.e. palms or other parts of the body, are determined by inherent properties of the vessels to react to the stimulus which provokes the change. This may be a genetic peculiarity though we have no proof that this is the case. In a few women observed in two or more pregnancies we have found a tendency for one or the other type of lesion to recur. There have been exceptions. Thus the supposition that there is only one mechanism at work in pregnancy which evokes vascular spiders or palmar erythema or both is far from established though the natural history of the phenomena points in this direction.

OTHER OBSERVATIONS

Although we did not see any clinical indication of hepatic disease complicating pregnancy, we carried out some liver function studies on 26 white women in the present investigation to see whether there was any laboratory evidence of impaired function, or any difference in those with vascular spiders or palmar erythema and those without such vascular changes. The icterus index, bromsulfalein retention (at 45 minutes after 5 mgm. per kgm.), cephalin-cholesterol flocculation and thymol turbidity tests were performed in the third trimester of pregnancy. Those tests did not reveal any significant sign of hepatic damage; and the very minor deviations from normal were found regardless of presence or absence of vascular spiders or palmar erythema or both. There

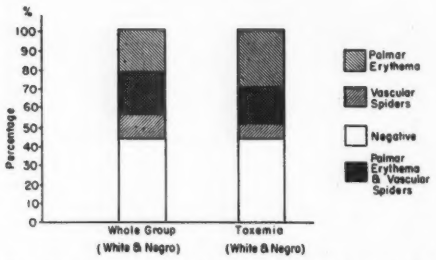

Fig. 18. A comparison of the incidence of vascular spiders, palmar erythema or both in women with toxemia compared with the whole group.

was no indication that damage to the liver comparable to that usually found in chronic cirrhosis, existed in the pregnant women in this study. Nothing suggested that vascular lesions in pregnancy have been caused by hepatic malfunction.

Although all the data have not been analyzed regarding age of the mother, number of pregnancies, sex and viability of offspring, and lactation with reference to the incidence and number of vascular spiders, and the incidence, type and degree of palmar erythema, our studies so far indicate no striking relationships. Thus the vascular changes in the skin had no notable association with first, or later pregnancies, with male or female offspring, with age or youth of the mother, with lactation or its failure to occur or to continue properly. We have studied hypertension and toxemias more extensively since there is some evidence and more belief that humoral factors play a part in their genesis. Patients having systolic blood pressure of more than 140 millimeters of mercury and diastolic blood pressure of more than 90 millimeters of mercury were classed as hypertensives. Hypertensive patients with albuminuria, edema, symptoms of headaches, etc. or convulsions in the third trimester of pregnancy were classed as toxemias. In 1,145 of the patients studied so far there were 24, or 2.1 per cent, with hypertension during pregnancy. In another 99, or 8.7 per cent, there was toxemia. These diagnoses were made by members of the obstetrical staff independently of our own studies, and the data were combined only after the records were complete. The number with hypertension was too small to have much significance, but even in this group the incidence of vascular spiders or palmar erythema, or the two in combination, was very nearly the same as in the whole group. Since the number with toxemia were larger we have compared the incidence of vascular spiders and palmar erythema in this group with the incidence in the entire series in Figure 18. While there are slight differences the figures agree so nearly that we conclude that the changes in the skin we have observed have no essential relation to toxemia or its absence.

GENERAL CONSIDERATIONS

The studies we have carried out indicate that vascular spiders and palmar erythema, alone or in combination, are found frequently as accompaniments of normal pregnancy. Since the investigation was intensive and persistent we discovered many lesions of which the subjects were wholly unaware. Many, however, were obvious and had been noticed, and in some persons they were the source of embarrassment or worry.

Since vascular spiders or palmar erythema may be found in normal nonpregnant women we have been particularly interested in their fate after pregnancy since our control observations do not include women in a wide range of ages who had never been pregnant. Such observations as we have made (Table I) indicate that a vascular spider may be found in about 10 per cent of white women who have borne children. In a study made by one of us during a nutrition survey of American troops in various islands in the Pacific during World War II it was found that vascular spiders were seen in 14.9 per cent of the white and in none of the negro soldiers. Even with these as a base line there is a marked and consistent increase in the number of women with vascular spiders and in the number of spiders per woman from the second or third month of pregnancy until term. At this time there is a sudden decrease in size of individual lesions, a complete disappearance of many so that by the seventh week after childbirth the number approaches that found in control groups. Subsequently there is a further decrease which apparently continues slowly so long as another pregnancy does not occur.

This study serves as a companion for similar investigations on vascular spiders and palmar erythema in persons suffering with chronic hepatic disease (4, 6). Although the number of patients with hepatic disease was relatively small it was ample to establish the fact that both spider nevi and palmar erythema may appear as complications of chronic or subacute disease of the liver. If and when the state of the liver improves these vascular changes may recede just as they do following the completion of gestation, though rarely with such dramatic suddenness. Vascular spiders in well established cirrhosis are usually larger and occur in greater numbers than in pregnant women. Their similar distribution over the upper part of the body, their similar shape, the palpable pulsation and intravascular pressure of 50 to 80 millimeters of mercury are strong indications of their kinship. We have not had an opportunity to observe a woman who had known of vascular spiders during a pregnancy who later had them with chronic liver disease nor have we encountered a woman with cirrhosis who became pregnant, though some with ascites suspected pregnancy. Nor have we compared the histologic picture of the lesions in cirrhosis with those of pregnancy. We are, however, convinced that there is no fundamental difference between those which appear in pregnancy and those which appear in cirrhosis. It has been suggested that a possible common factor in normal pregnancy and chronic liver disease might be a high level of circulating estrogenic hormones (3) or related endocrine substances, perhaps of adrenal origin (6). The fact that we have been able to find no significant abnormality of hepatic function in pregnant women with palmar erythema and vascular spiders as compared with those who do not have them suggests that disturbed liver function in pregnancy is not responsible for their occurrence.

As collateral testimony that estrogenic hormones may produce an effect on the vessels of the skin qualitatively similar to the well documented effect on vessels of the uterus, we have superimposed Venning's (27, 28) curve of estrogen excretion throughout pregnancy upon our figures for the incidence of vascular spiders and palmar erythema in white and negro

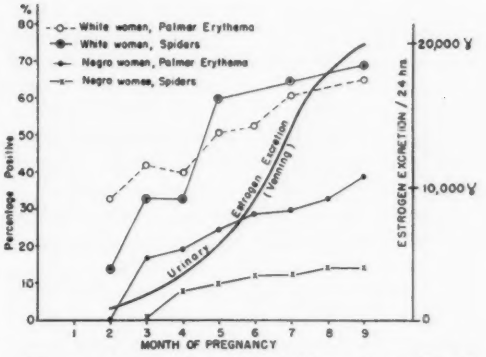

Fig. 19. A comparison of the incidence of vascular spiders and palmar erythema with the urinary excretion of estrogens (Venning) during pregnancy.

women during pregnancy (Fig. 19). Although the forms of the curves do not agree with precision there is a similarity. Evidence for the critical early months is inadequate for analysis. Crucial data in individual patients must be obtained in the future. There is, however, no established finding which invalidates the hypothesis that humoral agents with estrogenic function give rise to vascular changes in the skin during the course of normal pregnancy and during the active stage of chronic liver disease.

Our studies have established the rather surprising frequency of the vascular spider and palmar erythema as banal accompaniments of normal pregnancy. We have advanced the hypothesis that these phenomena may be caused by hormones, and have implicated the estrogenic substances in particular. The facts we have recorded should be known to obstetricians, if only for the occasional comfort they bring to women whose worry about such blemishes may add its needless burden to the trials of pregnancy. The speculations must stand or fall according to the results of hormone assays we now have under way.

SUMMARY

1. We have presented an interim analysis of data concerning the incidence, natural history, and fate of vascular spiders and palmar erythema as observed in 1,243 women in the obstetrical clinic of the Cincinnati General Hospital.

2. The literature on these cutaneous vascular changes has been reviewed. Vascular spiders apparently were first noticed as a benign complication of normal pregnancy by Corbett in 1914, and have been recorded by dermatologists and internists at intervals since then. The first note on palmar erythema of pregnancy which we have found was published by Feldman in 1939. No word about such lesions has been found in the American textbooks on obstetrics which we have consulted.

3. Vascular spiders have been found in about two-thirds of the white women and 11 per cent of the negro women during pregnancy. They tend to appear in the early months of pregnancy, especially during the second through the fifth months. They increase slowly in number and in size until term, or shortly before. About three-fourths of them have faded by the seventh week after delivery.

4. Details of the vascular spider of pregnancy have been presented in photographs of the involved skin before and after delivery and demonstrate the rapid return to normal.

5. Two types of palmar erythema have been described and photographs presented.

6. Almost two-thirds of the white women and slightly more than one-third of the negro women were observed to have palmar erythema during pregnancy. The appearance and the fading were more abrupt than with vascular spiders but the trends of appearance and disappearance were similar.

7. While the difference in incidence of the cutaneous vascular changes in white and negro women was large we have suggested that other factors than skin pigment alone may be involved. The depth of skin color is a major consideration. Vascular spiders and palmar erythema have not been reported in negroes during pregnancy heretofore.

8. Tests of liver function did not reveal significant abnormality, or differences between those with and without spiders or palmar erythema.

9. There was no marked difference in incidence or number of vascular spiders or of palmar erythema between subjects who later developed toxemia and those who escaped it.

10. We have compared the vascular spider of pregnancy with that found in chronic liver disease, and find no basic differences. They are apt to be larger and more numerous in persons with cirrhosis than in pregnant women.

11. We have advanced the hypothesis that vascular spiders and palmar erythema develop as a response to the stimulus of high levels of estrogenic substances circulating in the blood for long periods. Studies are in progress to test its validity.

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THORACIC COMPLICATIONS OF AMEBIASIS

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AMEBIASIS is a disease which is of interest to the internist, the general surgeon, and the surgeon who is limiting his practice to thoracic diseases. Although the disease in its incipiency is an intestinal infestation, there are complications which may require surgical relief. The treatment of the intestinal infestation is entirely a medical problem. The complication of an hepatic abscess, however, although best treated by medical measures should be conducted under the observation of a surgeon since surgical management of the abscess may become necessary if further complications set in. The hepatic abscess in turn may cause complications within the thorax which may require the services of a surgeon trained in the treatment of thoracic diseases. Surgery may be necessary to eliminate fistulous channels between the liver and bronchi left by the infection, to re-expand an imprisoned lung, or to remove damaged pulmonary tissue. Due to the increasing tendency to resect pulmonary tissue for pulmonary suppuration occasionally the diagnosis of amebic pulmonary suppuration may not be suspected until the time of operation. Now that more meticulous technique is possible in pulmonary resection and decortication the high mortality (33 per cent) previously reported by Ochsner and DeBakey (2) for surgery in this type of infection need not be feared. Four patients having thoracic complications of amebiasis treated during the past 2 years by various surgical procedures will be reported in this paper. Another patient having a complicating pericarditis from an amebic hepatic abscess who was treated by my associate will be briefly discussed. All of these patients have completely recovered from the hepatic abscess and its complications.

INCIDENCE

The general incidence of infestation with the Endamoeba histolytica is much higher in the general population than is usually realized. Statistics obtained from surveys a few years ago would probably not now be even high enough, since during the war so many men in the military forces saw service in areas where amebic dysentery was a very common disease. Craig estimated the prevalence of infestation in the population at large at from 5 to 10 per cent. There have been surveys that have cited the incidence as high as 33 per cent. Ochsner and DeBakey (3) in their writings upon this subject believe that an incidence of 20 per cent is a reasonable figure. It has been found that hepatic abscesses will complicate infestations with the Endamoeba histolytica in approximately 5 per cent of all cases. Furthermore, there will be complications within the thoracic cage in approximately 15 per cent of patients having hepatic abscesses. The sex incidence has never been adequately explained in the case of hepatic abscesses. Males predominate over females in the occurrence of this complication in a ratio of 15 to 1. The age incidence is also of some interest since it has been found that the majority of patients having hepatic abscesses fall between the ages of 20 to 50 years.

PATHOLOGY

Amebic abscesses of the liver undoubtedly occur due to the migration of the parasites through the portal system into the liver. Here the parasites clog the small capillaries and venules and set up a lytic process which destroys tissue. A small abscess develops and the necrotic zone of the liver tissue surrounding the abscess pours fluid and debris into the abscess cavity. The amebas are usually best found deep within the wall of the abscess very close to the healthy liver tissue. The abscesses are single in approximately 65 to 88 per cent of the cases (3). In cases in which the abscesses are multiple there may be coalescence of the abscesses but if this fails to occur the prognosis is much more grave. Approximately 85 to 96 per cent (3) of all hepatic abscesses of

From the Surgical Service of the Southwestern Medical College, Dallas, Texas.

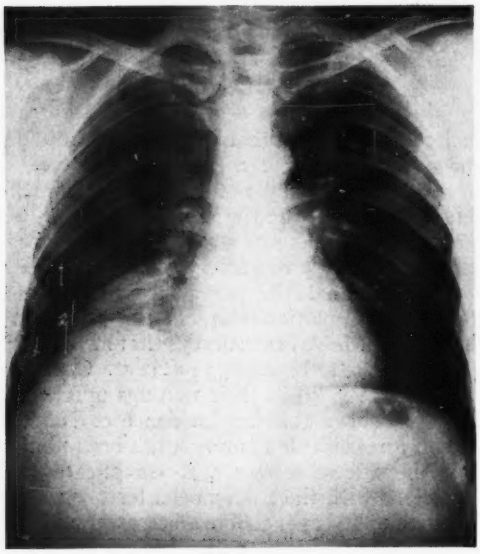

Fig. 1a.

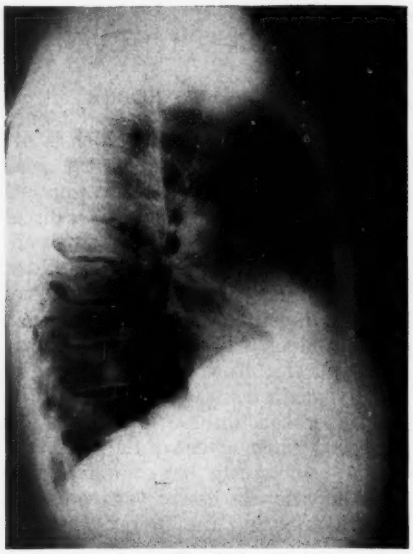

Fig. 1b.

Fig. 1c.

Fig. 1. Hepatic abscess which has ruptured into middle lobe. a, Elevated right diaphragm with dense shadow in right lower lung field. b, The middle lobe is contracted and the dense shadow within it blends into the shadow cast by the elevated liver and diaphragm. c, Iodized oil in sinus following drainage outlines both the hepatic and pulmonary cavities.

the liver are found within the right lobe of the liver probably because of the size of this lobe as compared with the left lobe. The thoracic complication comes about because of a direct extension of the abscess through the diaphragm into the pleural cavity or directly into the lung through adhesions that have been formed because of the inflammatory process. If the abscess is in the left lobe of the liver the extension of the abscess may be into the pericardial sac causing a pericarditis. Pleuropulmonary complications on the left seldom occur. There have been described in the literature solitary abscesses within the lung substance which are not adjacent to the diaphragm. It must be postulated that these abscesses are embolic in origin and that the amebas reached the pulmonary circulation by going through the hemorrhoidal veins into the vena caval system or by anastomotic channels between the venules of the portal and the vena caval systems within the liver. Abscesses of this type are the exception.

SYMPTOMATOLOGY

In approximately 50 per cent of all cases of pleuropulmonary complications from hepatic

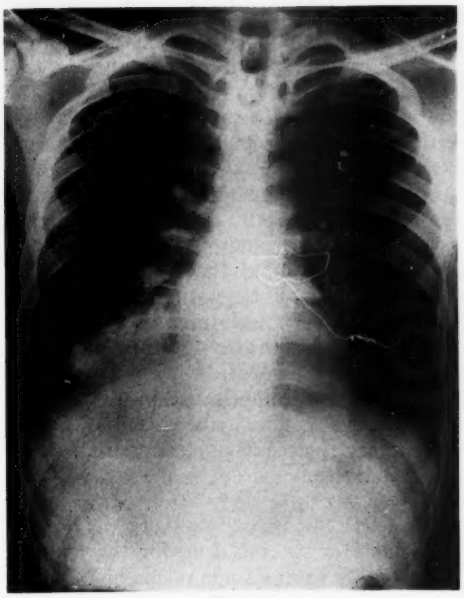

Fig. 2a.

Fig. 2b.

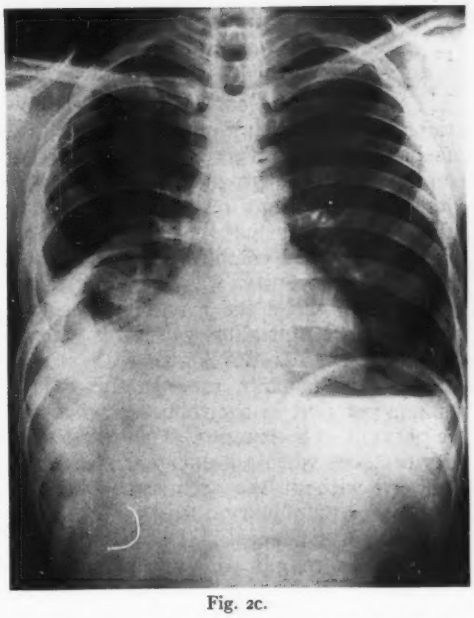

Fig. 2c.

Fig. 2. Hepatic abscess which has ruptured into right lower lobe. a, Posteroanterior view shows abscess in base of right lung. b, Lateral view shows the shadow cast by the pulmonary abscess to be continuous with the right diaphragmatic outline. c, Ten days following resection of lower lobe and repair of diaphragm.

abscesses there will be no history of a previous dysentery. The most usual complaint of a patient having a pleuropulmonary complication is pain in the lower right chest and in the shoulder. There is a cough which early is not productive. Later there is usually an episode of hemoptysis which then gives way to the coughing up of sputum which is described as being like chocolate or anchovy paste. A septic type of fever with or without chills will always be present. The patient also suffers from the usual signs of infection, i.e. anorexia, malaise, and weakness. There may be extreme weight loss.

ROENTGENOGRAPHIC APPEARANCE

The roentgenographic appearance of the chest is characteristic enough to be almost diagnostic in cases of thoracic complications from amebic hepatic abscesses. There is a hump like localized elevation of the diaphragm which is usually best seen in the lateral view (Figs. 2b and 4b). If there has been perfora-

tion of the abscess directly into the pulmonary tissue there will be present a shadow in the base of the involved lobe with the apex of the shadow tapering off toward the pulmonary hilum (Figs. 1b and 2b). There may or may not be an annular shadow with a fluid level indicating a pulmonary abscess depending upon the amount of pulmonary tissue destruction and whether the communicating bronchus will admit air to the pulmonary abscess. In case of a complicating empyema there will be the appearance of pleural fluid. A pyopneumothorax may be present at the time of the first examination if a bronchus is open into the pleural space. Since the lung is adherent to the diaphragm the collection of pleural exudate may be more lateral than basal (Fig. 3b). Loculation of the pleural exudate is a common occurrence with amebic empyema (Fig. 4a). An hepatic abscess in the left lobe of the liver can be suspected if a roentgenogram of the abdomen following barium by mouth reveals the stomach to be displaced posteriorly and laterally. A widened pericardial shadow would indicate possible rupture into the pericardial sac.

PROGNOSIS

The prognosis of pleuropulmonary complications of an hepatic abscess due to the Endamoeba histolytica vary with the type of complication. The prognosis is much more severe if an empyema results. Ochsner and DeBakey (2) reported that in a collected series of empyema complicating hepatic abscesses the mortality was 77.7 per cent. In their own series the mortality was 66.6 per cent. The mortality was lower when a pulmonary abscess developed without the occurrence of an empyema. In this case it was 42.2 per cent in the collected series and 22.2 per cent in their series. The lowest mortality occurred when a bronchohepatic fistula developed without the occurrence of either empyema or pulmonary abscess. There was a mortality of 10 per cent in the collected series in this type of complication and no mortality in the series reported by Ochsner and DeBakey. This mortality was greatly reduced when emetine therapy was given. In the 153 patients in the collected series with pleuropulmonary complications the mortality of 56.6 per cent when emetine was not used dropped to 9.1 per cent with emetine therapy. In the series reported by Ochsner and DeBakey (2) there was 60 per cent mortality without the use of emetine and no mortality when emetine was used. Ochsner and DeBakey (2) also further warned against unnecessary surgical drainage procedures in the case of hepatic abscesses and their pleuropulmonary complications. They showed that there was a 33 per cent mortality in the patients upon whom operations had been performed. They deserve much credit for pointing out the efficacy of emetine therapy in hepatic abscesses and their pleuropulmonary complications. With present techniques and with chemotherapy, however, surgery if necessary is safer than these authors indicate.

TREATMENT

Emetine is a specific drug for the hepatic abscess caused by the Endamoeba histolytica. Even after a pleuropulmonary complication has occurred, emetine should be used in an attempt to avoid surgery and in conjunction with surgery should surgical interference become necessary. Emetine is a drug which must be used with extreme care because of its toxicity for cardiac muscle. Under ideal conditions an electrocardiogram should be made before treatment is instituted. A course of therapy should then be instituted once the diagnosis of an hepatic abscess has been established giving 1 grain doses intramuscularly daily for 6 to 10 days. Following this course of treatment the electrocardiographic tracings should be repeated to determine whether or not there has been myocardial damage. If the patient also has signs of amebic dysentery, such drugs as carbarsone and diodoquin should be administered. It should be remembered, however, that this type of drug is toxic to the liver and should be used very cautiously if there are signs of extreme liver damage due to the abscess. In conjunction with the emetine therapy, the abscess cavity within the liver should be aspirated if this is possible. If there is tenderness and bulging of the lower costal margin due to the presence of the abscess, aspiration with a long needle with an

adequate lumen should be attempted in the most tender area. If pus is obtained, as much of the pus as possible should be aspirated. The aspiration of the abscess not only serves the purpose of evacuating the cavity but also draws fluid from the liver into the abscess cavity and by doing this also causes the amebas to migrate toward the abscess cavity where they in turn will be removed at a subsequent aspiration. This drawing of fluid into the abscess cavity also allows the emetine to come in better contact with the amebas within the wall of the abscess. Aspirations of the abscess cavity should be repeated until a significant amount of pus cannot be obtained. As a rule even though the hepatic abscess has ruptured through the diaphragm into the pulmonary tissue and has found an outlet through the bronchial tree the cough and expectoration will promptly cease after the evacuation of the abscess by aspiration and the treatment with emetine.

INDICATIONS FOR SURGERY

Surgical interference becomes necessary in amebic hepatic abscesses which have caused pleuropulmonary complications if: (1) secondary infection has occurred, (2) an empyema has resulted which cannot be cured by repeated aspirations, (3) a persistent abnormal channel between the bile duct system and bronchi persists, (4) fibrosis of pulmonary tissue as result of the abscess continues to be symptom-producing.

The most common indication for drainage of the hepatic abscess will be secondary infection. Once an abscess in the liver due to the Endamoeba histolytica has become secondarily infected by pyogenic organisms it must be drained. This drainage can usually be accomplished through an extraserous route. Complications within the peritoneum and pleura will be thus avoided. One of the most serious and annoying complications of drainage of an hepatic abscess is the gangrenous infection of the skin and subcutaneous tissue which may result. This complication occurred in Case 1 of the present report. If this complication results it is necessary to excise the gangrenous tissue entirely down to healthy tissue. This may require the excision of a considerable amount of skin and the raw surface may have to be covered by skin grafting at a later date.

Pleuropulmonary complications are usually best handled by thoracotomies employing reparative surgery without external drainage. In the case of an empyema which will not clear with repeated aspirations a thoracotomy can be done and a decortication of the lung and diaphragm performed. In the course of this decortication it will be necessary to close the opening in the diaphragm. As a rule, the hepatic abscess has erupted into the pleural cavity or pulmonary tissue in such a way that the abscess has practically healed itself. It is not necessary in these cases to employ subsequent counterdrainage for the hepatic abscess. Resection of damaged pulmonary tissue will be necessary. In most cases this will require no more than a wedge resection of the fistulous area. In other cases, however, it may be preferable to remove an entire lobe. After the products of the infection have been as cleanly removed from the chest as possible the pleural cavity should be drained with an intercostal drain connected to a negative pressure system. The chest is then closed.

Rupture of an hepatic amebic abscess through the pericardium into the pericardial sac is a serious complication and as judged by review of the literature has usually proved fatal. With prompt treatment recovery is possible. Aspiration of the pericardial exudate and emetine therapy should be carried out immediately. This may be all that will be required to bring about recovery. Other complications may ensue which will require surgery. My associate (4) while in the medical corps during the late World War had under his care a soldier who developed an hepatic abscess of the left lobe of the liver. The abscess ruptured into the pericardial sac and peritoneal space beneath the left leaf of the diaphragm. The subdiaphragmatic space was drained anteriorly. It was soon evident that the abscess had perforated the wall of the stomach and a gastric fistula resulted. Posterior drainage was later instituted through resection of the 9th and 10th ribs in the midaxillary line. Eventually the gastric fistula closed and all draining sinuses healed. Eme-

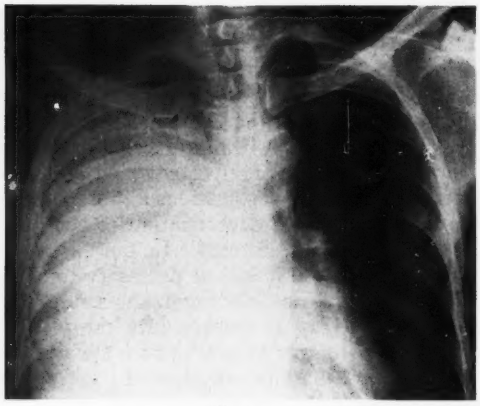

Fig. 3a.

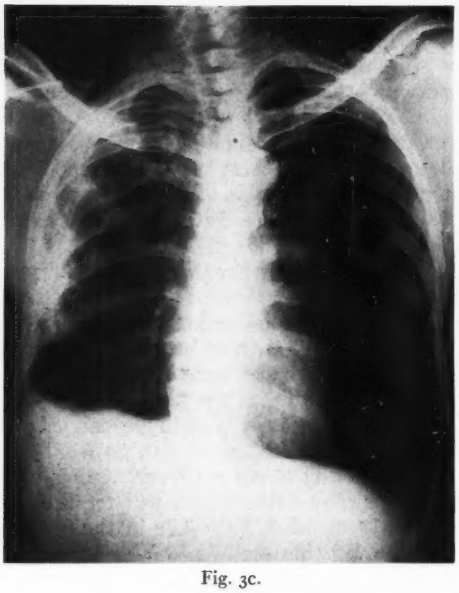

Fig. 3c.

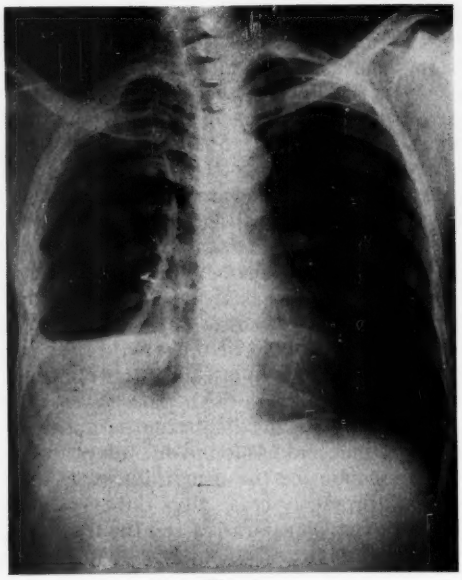

Fig. 3b.

Fig. 3. Empyema due to rupture of amebic hepatic abscess into right pleural cavity through anterior basal segment of the right lower lobe. a, Massive pleural effusion in right chest. b, Following aspiration of fluid and emetine therapy right lung fails to re-expand. c, Seven months following decortication lung has re-expanded to fill right hemithorax although considerable fibrothorax has resulted.

tine therapy along with sulfadiazine was used early in the treatment of the infestation but surgery became finally necessary to bring about complete recovery.

POSTOPERATIVE MANAGEMENT

If emetine therapy had not been used previously, either because a true diagnosis was not suspected or the urgency of the situation made it unwise to wait, it should be instituted postoperatively with the safeguard of careful studies of the myocardium as outlined. Following the course of emetine therapy it is usually advisable to give a course of carbarsone or diodoquin for the dysentery. The use of this subsequent therapy will depend upon whether or not amebas can be demonstrated in the stools.

CASE REPORTS

CASE 1.[1] C. T. H., aged 42 years, white male. This patient was admitted to Baylor University Hospital June 3, 1945 as a transfer from another hospital. At the former hospital an amebic abscess of the liver had been drained 2 weeks previously. At the time of the drainage of the abscess it had been found that the abscess had perforated the diaphragm into the right middle lobe. For 1 year previous to the original admission to the hospital the patient had complained of dysentery and had been seen by various physi-

[1]Case 1 was included in this report by the permission of Dr. Walton H. Cochran, his physician. This patient, although observed by the author, was not under his care.

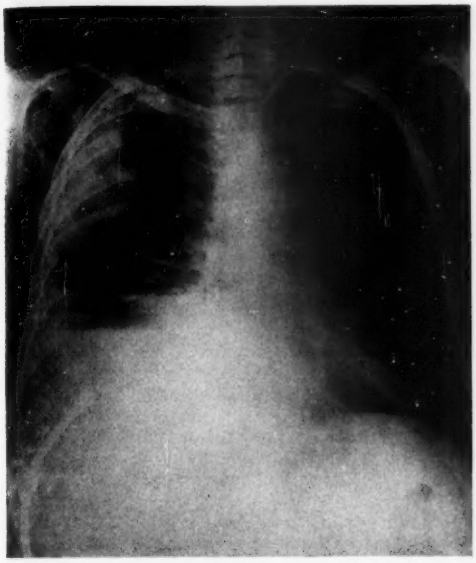

Fig. 4a.

Fig. 4b.

Fig. 4c.

Fig. 4. Empyema secondary to rupture of amebic hepatic abscess into right pleura. a, Loculated empyema right. Large hepatic abscess has been drained subcostally and catheter drain can be seen in place. b, Lateral view shows localized dome of diaphragm under anterior basal segment of right lower lobe. c, Empyema has cleared with drainage but fistula between hepatic abscess and bronchial tree remained causing repeated hemoptyses.

cians. At one hospital a diagnosis of carcinoma of the sigmoid colon had been made and resection of the colon was advised. The patient refused the operation and left the hospital against advice. The dysentery continued and he finally developed a severe pain in the anterior aspect of the lower right chest. He was admitted to a hospital and the abscess in the liver drained by the extraserous route. The patient was an adult male appearing chronically ill. There had been obvious weight loss. The physical examination was negative except for the region of the upper abdomen and lower right anterior chest. There was a transverse incision at the level of the 6th rib adjacent and lateral to its costal cartilage. Purulent material drained from this incision. Posterioranterior and a right lateral roentgen view of the chest showed a localized humping of the diaphragm anteriorly under the middle lobe (Fig. 1). The middle lobe was shrunken in size and only partially air containing. The patient continued to run a low grade temperature elevation and there appeared a gradual extension of induration and inflammatory reaction about the incision on the chest.

On the 28th of July the patient was returned to the operating room and the sinus tract was explored. At the bottom of the incision there was a small tract which led into the pleura. For about 4 to 5 centimeters on either side of the incision there was obvious involvement of the chest wall with a meaty infection. With the cutting current of the endotherm a wide oval section of skin and subcutaneous tissue

including the right nipple was excised. The underlying muscles were relatively healthy. The old sinus was opened and the degenerated portion of the 6th rib along with a portion of the 5th rib were excised. This laid bare a small cavity in the anterolateral and anterior portion of the right pleural cavity and a small abscess in the right middle lobe. The wound was packed with dry gauze. Pathological report showed amebiasis of the skin and subcutaneous tissue. Following the excision of the amebic abscess of the chest wall there was progressive healing and improvement and the whole wound finally healed without necessitating skin grafting. The patient has remained well.

CASE 2. H. P., aged 25 years, colored, male. This patient was admitted to Parkland Hospital on November 11, 1947. He gave a history of epigastric distress after meals for 10 months. Two months before admission he developed a dry nonproductive cough worse in the evening and at night. Five weeks before admission he quit work because of weakness. Three weeks later he had an episode of coughing up of blood and rust-like sputum. He had lost 25 pounds in weight during the previous 5 weeks. There had been no pain in the chest. Two years before there had been a period of 2 months when the patient had frequent episodes of pain around the umbilicus and left abdomen. This pain was relieved by eating or by drinking milk. The patient stated that he had the "bloody flux" for several months.

Physical examination revealed a chronically ill colored male coughing frequently. The right chest was slightly sunken and lagged during respiration. There was dullness on percussion at the right base posteriorly and in the axilla. Breath sounds were depressed in the right posterior chest and a few coarse râles could be heard. The patient was noted to have marked pulmonary osteoarthropathy. Roentgenograms of the chest revealed a dense shadow in the base of the right lower lobe adjacent to the mediastinum (Fig. 2). There was a fluid level indicating pulmonary abscess. The remainder of the lung fields were clear. A bronchoscopy was performed on the 26th of November. The tracheal mucosa appeared normal. There was a considerable amount of mucopurulent secretion coming from the right lower lobe bronchi. This secretion was not foul. The diagnosis was nonputrid abscess of the right lower lobe of lung.

On November 24 the right chest was opened following removal of the 7th rib. The pleural cavity was found to be free except where the lower lobe was densely adherent to the diaphragm. The structures at the hilum of the lower lobe were handled by dissection technique. The artery and vein were secured and severed. The bronchial stump was closed with individual sutures of No. 30 cotton. The dense adhesions to the diaphragm were then separated. In separating these adhesions the abscess in the base of the lung was broken into and it was found to have been caused by the eruption of an abscess in the liver through the diaphragm into the lower lobe. There was a large crater approximately 5 centimeters in diameter and 2 centimeters in depth in the liver. The diaphragm was drawn together with mattress sutures of No. 30 cotton. A drain was placed in the 8th interspace in the posterior axillary line and connected to a water-seal bottle. The chest was closed. Pathological report was: "Specimen consisted of right lower lobe of lung. In the base of the lobe surrounded by a large margin of normal appearing pleura there is a crater which is 7 by 6 centimeters in size and which extends up into the parenchyma of the lung for about 4½ centimeters. This cavity is lined by very friable necrotic shaggy shreds of grey to reddish brown tissue and a small amount of thick purulent greyish-green exudate is adherent to the wall. Communicating by an opening of .7 centimeter with the larger cavity is a smaller cavity 3.2 centimeters in diameter near the hilus. There is a smaller cavity of the same type of 2 centimeters in diameter near the base. The lung parenchyma is atelectatic and contains a small excess amount of blood. Microscopic examination of the sections of the lung revealing the abscess wall shows the latter to contain on its surface a small amount of eosinophilic debris containing a moderate amount of polymorphonuclear neutrophilic leucocytes. Lying in this eosinophilic debris loosely attached to the lining of the abscess cavity are present numerous large round and slightly oval bodies which are sharply demarcated measuring 25 to 35 microns in size. These possess slightly eccentric nuclei which are quite small and hyperchromatic and contain a central nucleolus. The cytoplasm is distinctly eosinophilic, rather opaque in appearance and usually contains either intact or hemolized red blood cells and other debris. These bodies are entirely characteristic of the trophozoites of Endamoeba histolytica." Pathologic diagnosis was chronic amebic abscess of the lower lobe of the right lung. The diagnosis of amebiasis with amebic abscess of the liver rupturing into the right lower lobe was made at the time of surgery. The patient was immediately started on a course of emetine hydrochloride grains ⅓ three times a day. In addition the patient received postoperatively 50,000 units of penicillin every 3 hours until the 18th postoperative day. The patient was discharged on the 20th postoperative day. The patient's temperature which had been running consistently between 102 and 103 degrees preoperatively dropped rapidly to normal on the second postoperative day, and remained normal until the time of discharge. The patient was discharged on the 20th postoperative day. He has remained well.

CASE 3. E. R., aged 23 years, colored, male. This 23 year old colored male was admitted to Parkland Hospital on October 29, 1946. He gave a history of pain in the right chest for 6 months and swelling of the right breast for 1 week. One month before he had had a hemoptysis. This spitting up of blood had persisted for 3 weeks following which the cough was productive of thick sputum which was clear. The pain in the chest was a constant sharp nonradiating pain aggravated by cough and deep inspiration.

There had been swelling of the ankles with the present illness. He had lost 10 to 12 pounds in weight in the last 6 months. The patient thought that he had had a daily fever. The past history revealed that the patient had had diarrhea beginning about 11 years ago. This had continued with about 4 or 5 daily stools until 9 months ago. The stools had contained blood.

Physical examination revealed lagging of inspiration on the right side of the chest with decreased fremitus and dullness to percussion on the right both anteriorly and posteriorly. There were coarse moist râles at the right apex posteriorly. The breath sounds were diminished over the entire right chest below the second rib anteriorly and posteriorly. Examination of the sputum revealed Endamoeba histolytica cysts and trophozoites. Examination of the stools revealed cysts and Endamoeba histolytica.

The admission roentgenogram of the chest showed total obscuration of the right hemithorax. Subsequent to aspiration of the pleural fluid it could be seen that the loculated pleural fluid was chiefly in the lateral portion of the chest and that the base of the lung was adherent to the diaphragm over most of its surface (Fig. 3). On admission to the hospital the patient was given diodoquin 9⅗ grains three times a day and emetine 1 grain intramuscularly daily. Several thoracenteses were done with aspiration of fluid from the right chest. The fluid was slightly turbid, thin and yellow in character. Examination of the fluid was negative for ameba.

On December 2, 1947, the right chest was opened through the 7th rib bed. A thick layer of fibrin was removed from the right lower and middle lobes. The anterior inferior segment of the right lower lobe which had been perforated by an abscess which came up through the diaphragm from the liver was excised. The diaphragm was closed without drainage. Pathological diagnosis was chronic, fibrinous, and fibrous pleuritis; chronic fibroid pneumonitis of lung. Following this operation the right lung expanded poorly so that on December 20 the chest was reopened and a redecortication was done. Following this procedure the lung slowly re-expanded. The patient was discharged from the hospital on January 20, 1947.

The patient was followed in the surgical out-patient clinic. On July 21 the patient was seen at which time he stated he was very well. He had no cough, and his general condition was good. X-ray examination showed complete reabsorption of the fluid. Examination of the stools at this time was negative for ameba. The patient was advised to do full work.

CASE 4. F. R., aged 50 years, white, male. This patient developed a severe dysentery while working as a civilian employee with the army on the island of Guam. He was returned to the United States for further treatment. Upon admission to the Lisbon Veterans Administration Hospital he complained of severe pain in the right lower chest and cough and expectoration of bloody material. The patient was febrile. There had been a noticeable loss of weight.

Physical examination showed the patient to be an emaciated white male of about the stated age. There was dullness to percussion over the lower two-thirds of the right chest both anteriorly and posteriorly. There was tenderness around the lower right costal margin.There was some appearance of bulging of the right anterior chest in the inferior portion and a fullness in the right upper quadrant of the abdomen. Around this area the patient was tender to palpation. Examination of stools and sputum revealed the Endamoeba histolytica. X-ray examination of the chest (Fig. 4) revealed a loculated hydropneumothorax on the right. There was a localized elevation of the diaphragm best seen in the lateral film. This elevation of the diaphragm was in the anterior chest. The pulmonary tissue above this elevation appeared dense and atelectatic. In subsequent x-ray examinations a fluid level could be seen in this region. Turbid yellow fluid was aspirated from the right chest. This fluid was later found to be purulent so rib resection drainage was instituted. At a later date a subcostal anterior drainage of the large liver abscess was carried out by the extraserous route. The patient gradually improved. The lung slowly re-expanded. All drains were removed and the sinuses healed. The patient suddenly began to have hemoptyses which although not sévere were annoying. It was evident due to bile in the sputum that there was a bronchobiliary fistula. A thoracotomy was advised for the purpose of breaking up this abnormal channel.

At operation on March 23, 1948, the right chest was opened through the 7th rib bed. The right pleural cavity was completely obliterated by adhesions which could be easily separated except around the previous drainage site and over the diaphragm. When the right lower lobe was separated from the diaphragm it was found that there was an opening through the diaphragm approximately a centimeter in diameter which led into a defect in the liver. The examining finger could be inserted through this opening into the hepatic cavity and counterdrainage was then secured through the previous drainage site through the anterior upper abdominal wall. A catheter was put in place and secured. The hole in the diaphragm was then closed. Examination of the indurated area in the base of the right lower lobe revealed a small abscess approximately a centimeter in diameter with a surrounding wall of infiltration. It was not thought necessary to remove this indurated area. Two mattress sutures were used to obliterate the small cavity. A drain was placed in the 10th interspace in the posterior axillary line and connected to a water-seal bottle. The chest was closed. The drainage tube was removed on the 2nd postoperative day since the lung was fully expanded. However on the 6th day it was evident that pleural fluid was reaccumulating. Aspiration yielded old blood indicating that there had been bleeding into the pleural space following removal of the intercostal drain. Drainage was reinstituted at the site of the original rib resection through the 9th rib. The patient gradually improved. The drains in the pleura

and hepatic abscess were gradually shortened and eventually removed. The condition of the patient is now satisfactory. There have been no recurrences of the hemoptyses.

CONCLUSIONS

1. Hepatic abscesses are common complications of amebic dysentery. These abscesses are best treated by emetine therapy and should not be treated surgically unless certain indications are present.

2. Pleuropulmonary complications of hepatic abscesses can in the majority of patients be successfully treated with emetine therapy.

3. Surgery will be required if: (1) the lung cannot be re-expanded, (2) a bronchobiliary fistula persists, (3) secondary infection occurs, and (4) when damaged pulmonary tissue produces a continued morbid state.

4. Formal thoracotomies with removal of as much of the products of the infection as possible are preferable to drainage procedures.

5. Proper surgical intervention should further lower the mortality and morbidity in this disease.

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CARCINOMA OF THE NASOPHARYNX

Report of 150 Cases

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CANCER of the nasopharynx is a highly malignant disease which has recently attracted the attention of pathologist and clinician. Usually the signs and symptoms of metastases from this growth have obscured the existence of the primary neoplasm; accordingly adequate descriptions of the natural history of nasopharyngeal cancer have been delayed.

Prior to the beginning of the twentieth century, very few references were found pertaining to this disease. Jackson in 1901 discovered only 13 cases in the world literature of which the earliest case report was in 1837. Not until 1921 was an adequate description of this type of cancer presented when Regaud and Reverchon, and Schminke published papers independently describing the pathologic features. Trotter in 1911 had described the classical Trotter's triad resulting from nasopharyngeal neoplasms which consists of impaired hearing, neuralgia of the second branch of the trigeminal nerve, and asymmetry of the soft palate.

Since 1921 excellent papers have been published including those of New 1922, 1925, 1931, and 1943; Furstenberg, 1938; and Martin, 1940. This report presents the pathological and clinical features of an unselected consecutive group of 150 patients with nasopharyngeal cancer who were treated at the Veterans Administration Hospital, Hines, Illinois, from 1931 to 1946 inclusive. The diagnosis in each instance was confirmed histologically.

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ANATOMY OF THE NASOPHARYNX

A brief review of the normal anatomy will serve better to explain the morbid processes. The nasal part of the pharynx is an irregular cavity with six walls, anterior, posterior, two lateral walls, a floor, and a roof. Anteriorly, it communicates with the nasal cavities through the choanae or posterior nares. The floor is formed by the upper surface of the soft palate. Seldom does cancer originate from the anterior wall or the floor.

Posteriorly, the wall slopes superiorly and anteriorly blending into the roof or fornix which lies below the body of the sphenoid bone and is attached also to the basilar portion of the occipital bone. Its mucosa is thrown into multiple folds and contains much lymphoid tissue ("adenoids").

The lateral walls contain the openings of the eustachian tubes. Behind the openings, the cartilage of the tube forms a prominent ridge, the torus. Superior and posterior to the torus is the pharyngeal recess or fossa of Rosenmueller, and directly above the upper end of the fossa of Rosenmueller is the foramen lacerum affording entry into the intracranial cavity.

Histologically, pseudostratified, ciliated, columnar epithelium ("respiratory" epithelium) is seen to line the nasopharynx, which changes into stratified squamous epithelium as one enters the oral part of the pharynx. There is an abundance of lymphoid tissue. Goblet cells and mixed glands of serous and mucous cells are present also.

Lymphatics. Because tumors of the nasopharynx produce early and extensive cervical metastases, a knowledge of the lymphatics of this region is of paramount importance. Lymphatic drainage of the nasopharynx is mainly into nodes in the retropharyngeal area and into nodes along the superior portion of the

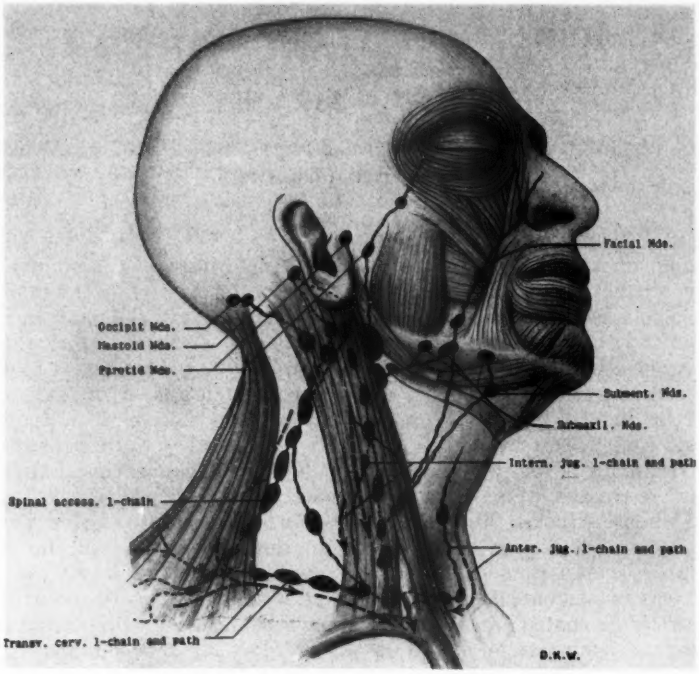

Fig. 1. Schematic representation of the lymphatic drainage and nodal connections of the face and neck. (After Rouvière.)

internal jugular vein (13). The collecting lymphatic trunks are very numerous and originate from the pharyngeal tonsil, the roof, posterior wall and lateral walls around the eustachian orifices. These combine and traverse the pharyngeal walls and usually terminate in the lateral retropharyngeal nodes; however, some terminate in nodes of the upper internal jugular chain. Some also may end in nodes further inferior or extend posteriorly and end in nodes along the spinal accessory nerve. Efferent channels from these nodes terminate in supraclavicular nodes. Hence, it can be seen why metastases from cancer of the nasopharynx may appear anywhere in the cervical region (Figs. 1 and 2).

INCIDENCE

During the 16 year period from 1931 to 1946 inclusive, there were 19,976 patients with primary malignant tumors admitted to Veterans Administration Hospital, Hines, Illinois. Of this group 1,299 neoplasms were found involving the upper digestive and respiratory tract (exclusive of lip). Intra-oral carcinoma thus comprised 6.3 per cent of all malignant neoplasms. Carcinoma of the nasopharynx represented 11.5 per cent of all intraoral cancer and 0.7 per cent of all patients admitted to this hospital bearing malignant tumors. Martin (8) observed that cancer of the nasopharynx represented 2 per cent of all malignant growths at Memorial Hospital.

ETIOLOGY

Age. An accurate picture of the true age and sex incidence of nasopharyngeal carcinoma cannot be obtained from the records of a veterans hospital because of the select group of patients admitted. The average age of this series was 45 years; the youngest patient was 19 years and the oldest was 68 years. In 32

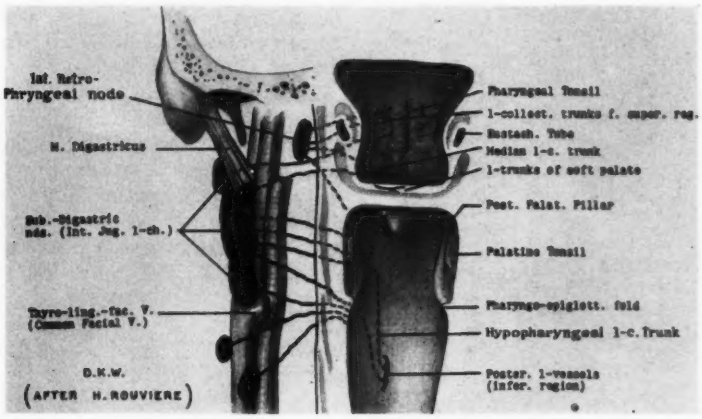

Fig. 2. Schematic representation of the lymphatics of the pharynx and their nodal connections. (After Rouvière.)

patients (21.3%) the age was below 40 years. Only 5 patients (3.3%) were over 60 years old. Because this disease occurs in patients who are relatively young, the need for considering cancer of the nasopharynx in younger age groups is emphasized. Cancer of the nasopharynx occurs in children and in adults below 30 years more often than any other malignant growth of the upper respiratory and alimentary tracts (8).

Sex. The sex was exclusively male in this series. Other authors describe a marked predilection (80%) in the male sex for this disease entity (8, 9).

Race. In this group 88 per cent of the patients were white and 11.3 per cent were negro. The percentage of negro patients hospitalized at this institution for all causes is 15 per cent. Therefore, the percentage of colored patients who had cancer of the nasopharynx does not differ significantly from the overall admission rate of negroes. One patient was Chinese, an incidence of 0.6 per cent of the entire group. Certain authors have described a high preponderance of nasopharyngeal carcinoma among the Chinese. Because of the select group of patients admitted at a Veterans Hospital for therapy, one would not expect a high admission rate of Chinese individuals.

Other factors. In the quest for certain factors which might have significance etiologically, analysis in this series was made of alcohol intake, smoking, and syphilis.

From our study, one cannot say that either tobacco or alcohol contributes toward the production of cancer of the nasopharynx. A study of the incidence of syphilis revealed that 11 (7.3%) of the entire group had syphilis. No significance is attached to syphilis as an etiological factor, since 5 per cent of all patients admitted to the hospital have positive Wassermann reactions.

A study to ascertain whether chronic infections, tonsillitis, or other infective or metabolic abnormalities contributed to the production of nasopharyngeal malignant neoplasms was found to yield negative results.

PATHOLOGY

Gross pathology. Nasopharyngeal carcinoma usually manifests itself early as a slight bulge or ulceration. It may originate in the irregular folds of persistent lymphoid tissue frequently present in the nasopharynx; usually in the fossa of Rosenmueller. This tiny lesion is frequently the source of massive cervical metastases. Not infrequently no demonstrable lesion is present and from 1 month to 2 years may elapse before the lesion becomes manifest.

As the tumor grows it may fill completely the nasopharynx with a bulky, fungating, friable mass or the lesion may be infiltrative and ulcerating.

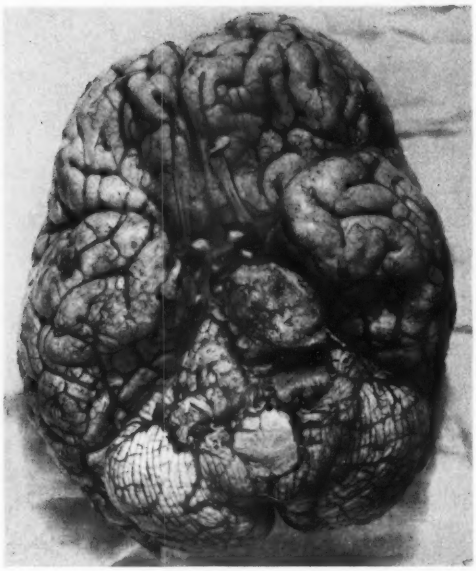

Fig. 3. Extension of nasopharyngeal carcinoma along base of brain with displacement of intracranial structures.

Location. Twenty-six patients (17.3%) of the 150 cases presented lesions in Rosenmueller's fossa. The next most frequent site was the posterior pharyngeal wall which was noted in 18 patients (12%) of which 6 (4%) were in the midline. The pharyngeal tonsil was the probable site of origin of the group that presented posterior pharyngeal wall lesions. The lateral wall (other than Rosenmueller's fossa) was the initial seat of the carcinoma in 10 patients (6.7%). A bulky cauliflower type of lesion filling the entire nasopharynx was described in 10 patients upon admission. Nine patients (6%) presented their initial lesion on the vault or roof. In 59 patients (40%) the exact location of origin could not be ascertained. This series, therefore, indicates that the most common site of origin of nasopharyngeal carcinoma is the lateral wall including the fossa of Rosenmueller.

The side involved was noted in all but 12 patients. In 42 cases (28%) the right side was involved; in 39 cases, the left side. In 57 patients (38%) both sides were involved.

Histology. Considerable controversy exists concerning the pathogenesis and nosology of neoplasms arising from the nasopharynx (8, 12,14,15). We have adopted Stewart's classification (8).

In this series, epidermoid carcinoma comprised 34.7 per cent and transitional cell carcinoma 30.7 per cent. Anaplastic carcinoma was observed in 14 patients (9.3%) and in 8 instances (5.3%) the neoplasm was unclassified. Although certain anaplastic and unclassified neoplasms resembled lymphosarcoma it was felt that sufficient criteria were not present to warrant that histologic classification. During the same period 5 nasopharyngeal fibromas, 2 plasmocytomas, and 2 adenocarcinomas of salivary gland origin were observed.

INTRACRANIAL EXTENSION

Extension of the tumor extradurally into the intracranial cavity frequently causes a host of neurologic symptoms duplicated by few other disease entities. In 2 cases in this series all cranial nerves were affected. The proximity of the foramen lacerum to the superior lateral wall of the nasopharynx affords an easy path for the cells to ascend and extend beneath the dura, stripping it from the base of the skull. In no case in our series was invasion of the dura observed.

Bone erosion may occur from pressure of the tumor or because of stripping of its nutrient periosteum from the bone by the spreading cancer. This was observed in 6 postmortem examinations in this series. The cranial nerves are affected usually by pressure and not by actual invasion (Fig. 3).

As the neoplasm extends forward, the inferior orbital fissure may be invaded producing proptosis and pressure on the optic nerve may produce blindness. Only in terminal stages is papilledema or other evidence of increased intracranial pressure observed.

The brain was damaged apparently due to pressure in 6 cases. Of this group two had softening of the frontal lobe, the cause, seemingly, of personality changes not infrequently noted in victims of this type of cancer.

Upon admission, 44 patients (29.3%) had involvement of one or more cranial nerves. After admission 11 additional patients (7.3%) developed the symptoms of cranial nerve involvement. Freedom of any cranial nerve

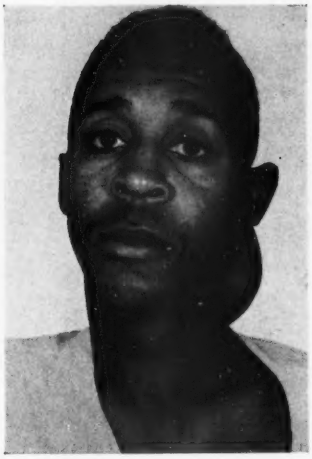

Fig. 4. Unilateral metastatic upper cervical nodes from a nasopharyngeal carcinoma.

Fig. 5. Voluminous bilateral metastases to cervical nodes from nasopharyngeal carcinoma.

involvement was noted in 95 patients (63.3%).

The abducens nerve was the one most frequently involved (24%) because of its location over the foramen lacerum. The second most commonly involved nerve was the hypoglossal as observed in 28 patients (18.6%), due usually to compression of the nerve as it emerges from the skull through the hypoglossal canal.

The trigeminal nerve was the third most commonly affected cranial nerve as noted in 26 cases (17.3%). Next in order were the vagus and glossopharyngeal nerves with 24 cases (16%) and 23 cases (15.3%), respectively. These nerves were compressed usually as they emerged through the jugular foramen by cervical metastases rather than extension of the tumor within the skull. The oculomotor nerve was sixth in order with 18 patients (12%) demonstrating ophthalmoplegia. The seventh and eighth nerves are well protected within the internal auditory canal of the petrous temporal bone, but when the facial nerve exits through the stylomastoid foramen, it may be compressed by enlarged lymph nodes. Seventeen instances of facial paralysis were noted (11.3%). Only 4 patients had auditory nerve findings (2.6%). The optic nerve tract was affected in 7 patients (4.6%). Only 2 instances of involvement of the olfactory nerve were noted. The tumor was very extensive in each case, and all of the 12 cranial nerves were involved. A Horner's syndrome was observed in 26 instances (17.3%).

CERVICAL METASTASES

Upon admission, 125 patients (83.3%) presented cervical metastases. In an additional 5 patients (3.3%) metastases developed after admission. Thus 86.6% of all patients developed cervical metastases and in only 20 patients (13.3%) were no cervical metastases observed. In 67 of the cases (44.7%) bilateral neck metastases developed.

Any of the cervical chains may be involved and not infrequently all chains are invaded. The upper deep cervical lymph nodes were most frequently involved in this series (Figs. 1 and 2), and submental and submaxillary node involvements were only infrequently encountered.

Generalized metastases. Of the 37 autopsies obtained from 128 deaths there were 9 (24.3%) who had extension to the intracranial cavity. Of this number 4 patients did not have cervical metastases. Intracranial extension may

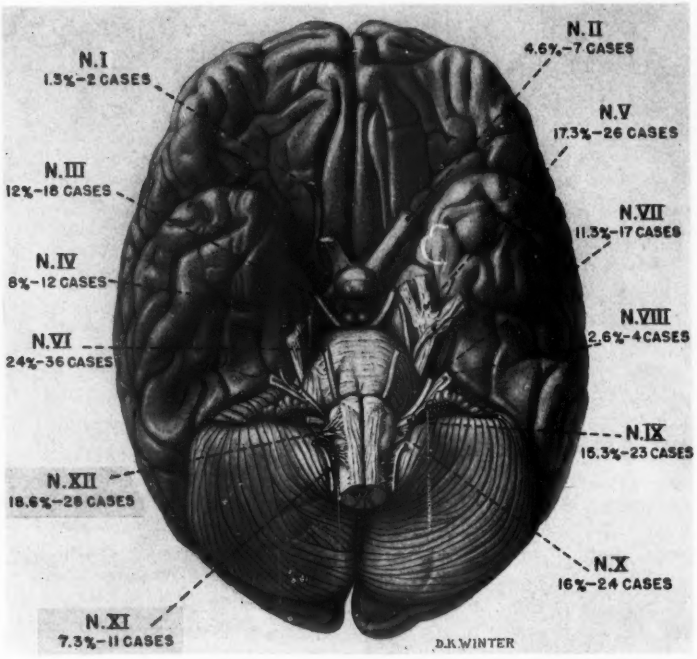

Fig. 6. Basal view of the brain with cranial nerves showing incidence of each cranial nerve involvement. (Courtesy Blakiston Co.)

occur without cervical metastases. Twenty patients (54%) had generalized metastases. The liver (15 cases) and lungs (9 cases) were the most frequent visceral organs involved.

Generalized metastases occur more frequently from nasopharyngeal carcinoma than from any other intraoral cancer. It was observed in only 13.9 per cent of 72 autopsies on patients with carcinoma of the tongue at this hospital (unpublished data).

SYMPTOMS AND CLINICAL COURSE

Initial symptom. Nasopharyngeal carcinoma develops insidiously and rarely presents initial symptoms due to the primary growth. Symptoms from cervical metastases and intracranial extension usually focus attention upon the existence of the neoplasm. In this series of 150 patients it was noted that the most frequent symptom was swelling of the neck, observed in 73 instances (48.7%). Pain of the side of the face and head was the initial symptom in 19 instances (12.6%). In only 6 patients (4%) was nasal obstruction a presenting symptom with an additional 3 patients (2%) who had associated deafness and epistaxis.

The ear was involved in 11 patients of this group (7.3%) who had a presenting complaint of earache, deafness, and tinnitus. In 7 patients (4.7%) the first symptom noted was referable to the eye and patients complained of poor vision, pain, or diplopia. In an additional 4.7 per cent of the entire group, various miscellaneous symptoms were present, including loss of weight, paralysis of the lower legs due to spinal cord metastases, and difficulty in talking.

Physical signs. In addition to bulky cervical metastases, the physical signs usually result from pressure of the tumor upon contiguous structures. Conduction deafness was observed in 48.6 per cent of all patients. Signs referable to cranial nerve involvement were observed in 36.7 per cent of all cases.

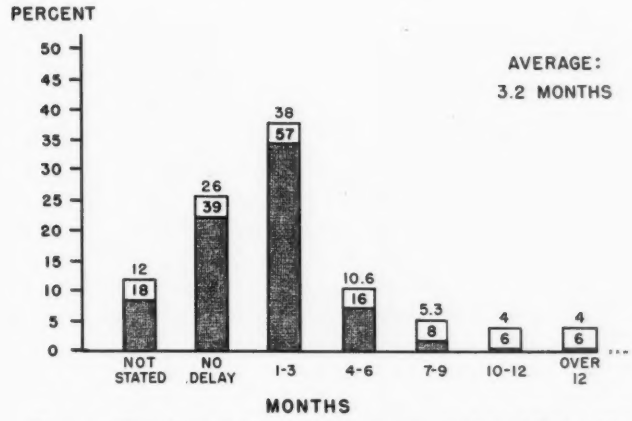

Chart 1. Time interval from date of symptoms to date of first seeking medical attention.

Involvement of several cranial nerves may produce a Gradenigo syndrome (1) or Trotter's triad. When metastases to cervical lymph nodes are marked or lateral extension occurs, the jugular foramen syndrome is found as the ninth, tenth, eleventh, and twelfth nerves and the cervical sympathetics are paralyzed. One observes weakness and asymmetry of the soft palate with loss of the gag reflex. Loss of taste on the posterior third of the tongue is present and the patient complains of dysphagia and accumulation of secretions in his pharynx. Passage of food into the lower respiratory tract occurs with consequent cough. Hoarseness may be noted due to paralysis of one vocal cord.

DIAGNOSIS

The disease is protean in its manifestations and may imitate many other neurological, otolaryngological, and ophthalmological conditions. Description of nasopharyngeal cancers can be found in journals relating to the nervous system (4, 9, 18), the ear, nose, and throat (8), the eye (2), as well as in journals of pathology (16), radiology (7) and general surgery (1). Early, the symptoms are referable to areas other than the nasopharynx and accordingly the diagnosis is missed frequently. In this series the correct diagnosis was not suspected by the referring physician in 92 patients (61.3%). The following diagnoses were the ones erroneously made by referring physicians: inflammatory lesions, 28 patients; cervical Hodgkin's disease, 20 patients; primary cervical carcinoma, 8 patients; cerebellopontile angle tumor, 1 patient.

Other diagnoses included organic brain disease, central nervous system lues, neck abscess, otitis media, and chronic sinusitis.

Previous to admission, 21 operative procedures had been performed on 19 (12.7%) patients in this series in the presence of the un-

Fig. 7. Horner's syndrome and deviation of tongue to side of lesion (twelfth nerve) in a patient with a nasopharyngeal carcinoma. Note: smaller pupil and ptosis of upper lid, right eye.

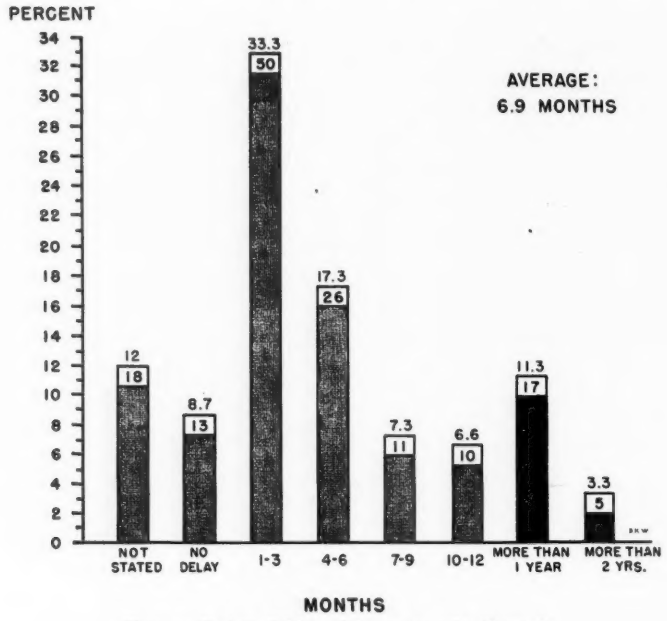

Chart 2. Period of delay of doctor to make diagnosis.

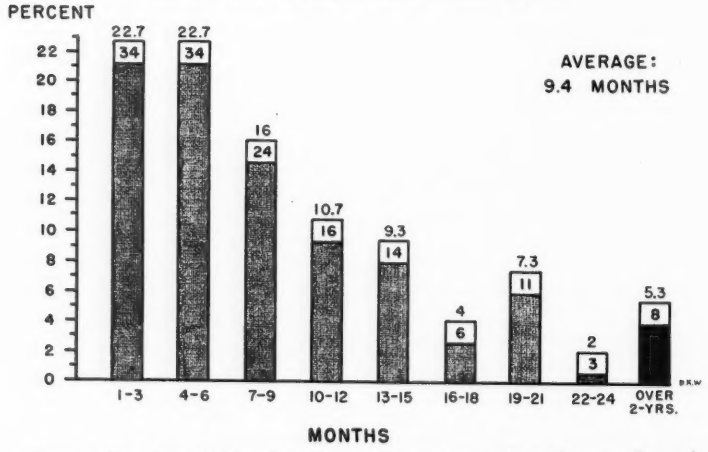

Chart 3. Time interval from date of onset of symptoms to date of correct diagnosis in 150 cases.

suspected nasopharyngeal carcinoma. There were 7 tonsillectomies, 3 mastoidectomies, 3 multiple teeth extraction, 2 instances of incision and drainage of neck abscesses, 4 intranasal polypectomies, 1 radical sinus resection, and 1 paracentesis of the ear drum.

DELAY IN DIAGNOSIS

In 39 cases (26%) the patient sought medical attention within 1 month after onset of symptoms. In Chart 1, this group of patients is considered as showing no delay in seeking medical attention. The average lapse of time

Fig. 8. Irradiated skin reaction demonstrating location of lateral facial portals.

Fig. 9. Irradiated skin reaction demonstrating location of infraorbital portals.

before the patient applied for medical care was 3.2 months. Twenty patients (13%) delayed over 6 months.

After the first visit to the physician, an average lapse of 6.9 months occurred before the correct diagnosis was made by the doctor (Chart 2). In 13 patients (8.7%) the diagnosis was made within the first month, this was considered as no delay. In 22 patients (14.6%) more than 1 year was required by the physician to make a correct diagnosis.

Chart 3 demonstrates that the average time interval from the onset of symptoms until the correct diagnosis was established was 9.4 months. In 42 patients (28%) the diagnosis was made after a lapse of 1 year following onset of the first symptom. In only 34 patients, or 22.7 per cent, was there a delay of less than 3 months.

DIFFERENTIAL DIAGNOSIS

Cancer is the most frequent lesion of the nasopharynx in the adult. A careful examination of the nasopharynx using a soft palate retractor and a curved mirror aided by finger palpation will permit the taking of a biopsy of any suspicious area. It is emphasized again that the lesion may be small and covered frequently by hypertrophied lymphoid tissue. Accordingly any irregularity or firmness warrants a deep bite with the biopsy forceps.

All children and young adults who have undergone resection of "*adenoids*" should be examined for possible neoplasia.

Nasopharyngeal fibroma, found in adolescent males, involute as maturity is reached. These tumors are characterized by a smooth surface and very profuse bleeding. Other tumors which have been described in this location are salivary gland tumors, chordomas from the primitive notochord, craniopharyngiomas from Rathke's pouch and plasmocytomas. To a less extent are found teratomas of the epipharynx, hemangiomas, lymphangiomas, choanal polyps, and retropharyngeal lymph node tuberculosis.

Rarely does a tumor of the pituitary gland extend into the postnasal space. The differential diagnosis here is particularly important to avoid a possible craniotomy.

In all metastatic cervical neoplasms, in which no primary lesion has been discovered, careful scrutiny of the nasopharynx should be performed repeatedly. Nasopharyngeal carcinoma is one of the most frequent lesions which remains quiescent but produces early metastases.

Neurological symptoms occur early and frequently and should invite a careful examination of the nasopharynx.

Frequently the patient is not carefully studied and is referred for neurosurgical intervention. Concerning this feature Davis and Martin state:

"We believe ... it is usually evidence of carelessness on the part of some examiner at

a b

Fig. 10. a and b, Nasopharyngeal carcinoma with intracranial extension and bilateral abducens nerve paresis before intensive irradiation. Portals for treatment are outlined.

a b c

Fig. 11. a, b, and c, Disappearance of abducens nerve paresis following irradiation. Note: Skin changes from deep x-ray treatment. Same patient as shown in Figure 10, a and b.

some time during the course of the patient's history, if the patient arrives in the hands of the neurologic surgeon with signs of intracranial extension from a nasopharyngeal tumor which is only then recognized for the first time."

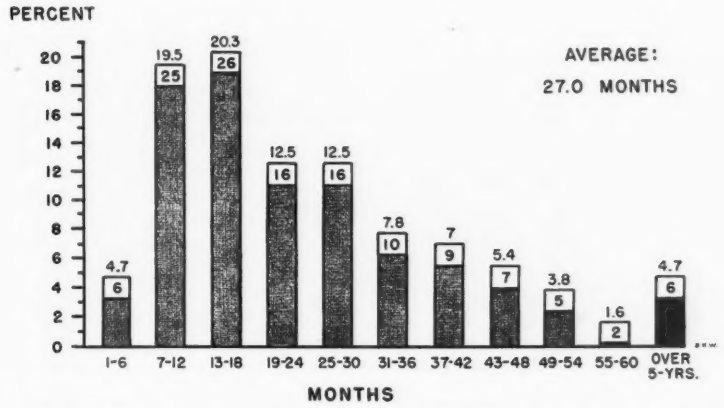

Chart 4. Time interval from date of onset of symptoms to date of death in 128 deaths.

Roentgenograms have not been of significant aid in establishing the diagnoses and radiological evidence of bone destruction was noted in 6 cases of this series.

A biopsy should be taken always of any suspicious area to establish the diagnosis.

TREATMENT

Therapy of cancer of the nasopharynx is exclusively irradiation, and all patients in this series were so treated. The early metastases, the anatomical inaccessability, and the undifferentiated features of the disease obviate success with surgery.

The patient's general condition during roentgentherapy must receive paramount consideration, and maintenance on an adequate caloric intake supplemented with vitamins is essential. An oral hygienist should administer local hygienic measures before and during therapy.

Treatment of the primary lesion. Fractionated x-radiation is recommended. The following factors are now utilized: 200 to 250 kilovolts, 50 to 60 centimeters target skin distance, a filter of 0.05 to 1 millimeter of copper, and 4 to 6 milliamperes. The field size varies from 6 to 8 centimeters in diameter. The ports used are two lateral fields which may be combined with anterior infraorbital fields. A dosage of 200 r to each of two ports daily is given until about 3500 r, times two, have been administered. Supplemental therapy may include an additional 1000 milligram hours with the Martin-Blady nasopharyngeal radium applicator (8) (Figs. 8 and 9).

Treatment of the metastases from nasopharyngeal cancer. Patients that have metastases high in the neck, may be treated through a portal which will include both the primary neoplasm and the cervical metastases. In most instances, too large a portal would be necessary so it is better to treat the primary as a separate entity and utilize a separate port for the cervical metastases. Externally applied deep x-radiation therapy is preferred for the metastases. We believe with Martin (8) that it is advisable to limit the size of the port and treat only the visible metastatic lesions instead of using large ports which will cover the entire cervical area. A dose of 4000 to 5000 r measured in air may be administered. At the completion of this dose if any of the disease persists, radon seeds (5 to 8 threshhold skin erythemas) may be administered interstitially.

Following the first treatments of radiotherapy, a rapid diminution of the severity of the symptoms occurs and cranial nerve paralyses may entirely disappear (Figs. 10 and 11). Distant metastases should be treated with deep roentgen therapy and the dose determined by the symptomatic response. Small doses (750 to 1000 r) may frequently produce marked improvement.

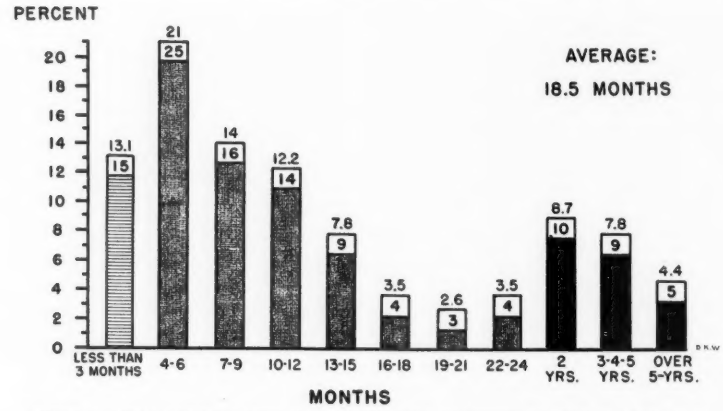

Chart 5. Period of time from date of adequate treatment to date of death in 114 cases.

END RESULTS

Of the 78 determinate patients, 71 have succumbed of the cancer making the net 5 year survival rate 9.8 per cent. Of the 71 patients who were treated too recently for a 5 year evaluation, 56 have succumbed already of the disease. The average duration of life from onset of symptoms of the 128 patients that succumbed was 27 months (Chart 4).

In 7 patients where no therapy was administered the duration of life was 17 months from the onset of symptoms. In 89 patients that died following x-ray therapy the average duration of life from onset of symptoms was increased to 31 months (Chart 4).

Palliative irradiation therapy to the metastases (7 patients) or exclusively to the primary neoplasm (25 patients) did not significantly increase the life span—21 months and 20 months respectively—but did produce always marked palliation (Chart 4).

The best results were obtained in patients in the fourth decade of life. The older age groups revealed the poorest survival rates.

The presence of cervical metastases altered the survival rate, although cures were obtained in patients with unilateral cervical metastases but none when the metastases were bilateral.

No patient with intracranial involvement survived the 5 year period. This complication accordingly offers the gravest prognosis.

In comparison with our 5 year survival rate of 9.8 per cent, Nielsen states that of 37 cases of nasopharyngeal malignancy 9 (24%) were symptom-free after 5 years. Martin and Blady (8) reported 20 survivals out of 80 patients (25%). Godtfriedsen collected 266 cases and reported 59 (22%) living after 5 years. New and Stevenson state they have had 13 per cent survival in 271 cases. Furstenberg had 40 cases of the disease and had only one survival at the expiration of 2 years. Kasabach reported on 42 cases with 14 (33%) living 3 or more years and 7 (16.6%) of those free of the disease 5 or more years.

SUMMARY AND CONCLUSIONS

Malignant lesions of the nasopharynx are much more common than statistics reveal because of the frequency of misdiagnosis. The nasopharynx is difficult to examine and the symptoms falsely indicate that the origin of the disease entity is located elsewhere. In the series presented in this paper, 150 consecutive, unselected cases from Hines Veterans Administration Hospital were reviewed and studied. In each patient biopsy from the nasopharynx was positive. All the patients were males, with an average age of 45 years. Most common site of origin was Rosenmueller's fossa in 26 cases (17.7%) of the 150 patients. Of the 150 cases there were 128 deaths with 37 postmortem examinations. Extension in-

tracranially was demonstrated in 9 (24%) of the autopsies and metastases below the level of the clavicle occurred in 20 instances (54%). A characteristic of the disease is early cervical metastases which was found in 125 patients upon admission (83.3%). Only 20 patients (13.3%) failed to demonstrate cervical metastases during the course of the disease.

Neck swelling was the most common initial symptom occurring in 79 patients (52.7%). Next was pain on the side of the face and head which occurred in 25 patients (16.6%). Rarely did initial symptoms referable to the nasopharynx occur.

Cranial nerve findings were seen in 44 patients (29.3%) upon admission, the sixth nerve was involved most often. A total of 55 patients (36.6%) had cranial nerve paralysis sometime during the course of the disease. Horner's syndrome was observed in 26 instances (17.3%).

The patient waited an average of 3.2 months after symptoms began before visiting a doctor. An average of 6.9 months elapsed before the physician made the correct diagnosis. A period of 10.1 months elapsed in the average case after a significant symptom commenced before adequate therapy was instituted. In the 128 patients that succumbed, an average time interval of 27 months occurred from the date of onset of symptoms to death. With adequate treatment, the time interval averaged 31 months from onset of symptoms to death. When no irradiation was administered the patients lived an average of 17 months. With treatment of the metastases alone because of the erroneous diagnoses or for palliation, an average time of 21 months was found from symptoms to death.

Prior to admission to Hines Hospital, the correct diagnosis was made by referring doctors in only 58 instances (38.7%).

Of the 78 determinate cases, only 7 remained free of the disease for 5 or more years. The net 5 year survival rate was 9.8 per cent. All the cures occurred in patients who had developed cervical metastases. No cures were obtained in cases with intracranial extension.

The treatment is exclusively radiological.

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UNCOMMON TUMORS OF THE SALIVARY GLANDS

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So much emphasis has been placed on the mixed tumor of salivary gland, and its malignant phase, the carcinoma, that other neoplasms arising in the salivary glands have received little attention. Nevertheless, there are less common growths arising in these organs which deserve consideration.

Several different varieties of histologically proved tumors which may originate in salivary gland are represented in the following group of case reports. The essential data of each case will be given, followed by a discussion.

CASE 1. M. C., a 35 year old female, had bilateral masses around the angles of the jaws for an uncertain period of time. The one on the right side was the larger. On physical examination there was a firm, discrete, nodular mass measuring 4 by 2.5 by 2 centimeters, lying in the region of the right parotid gland. The preoperative diagnosis was mixed tumor. The surgeon removed a poorly encapsulated tumor measuring 3.5 by 2 by 1.5 centimeters. The surface of the gross specimen was covered by tags of fat. On section there were several cysts ranging up to 1.5 centimeters in diameter. These were filled with turbid brown fluid. The remainder of the structure was composed of two lobules of deep brown, opaque, soft, smooth tissue. Well preserved normal parotid gland was easily found on histologic study. However, the greater part of the tissue was composed of large encapsulated masses of cells arranged in the form of abortive acini or in tubular fashion. The supporting stroma was a delicate meshwork of fibrous tissue. The cells were large, uniform, round to oval with clear or vacuolated cytoplasm and centrally placed blue vesicular nuclei. None of the cells was atypical, and there was no evidence of increased mitotic activity. In some areas the tumor was separated from normal tissue by a fibrous capsule of varying thickness. In other areas there was no distinct demarcation between normal and neoplastic tissue. Ducts were absent in the neoplastic portions of the specimen, but were normal elsewhere. The pathologic diagnosis was adenoma of the parotid gland. Figure 1 shows the disarranged acini of adenomatous tissue separated from the normal gland by a thin fibrous capsule.

The Department of Pathology of Northwestern University and the Laboratory of Pathologic Anatomy of Passavant Memorial Hospital, Chicago, Illinois.

CASE 2. A. B., a 62 year old white woman, had a discrete tumor in the right preauricular region the size of a "nutmeg," clinically interpreted as a mixed tumor of the parotid gland. This mass was hard and fixed to the angle of the jaw. At operation the tumor was found to occupy the posterior part of the right parotid gland. It was encapsulated but its removal necessitated the excision of some normal gland tissue.

The surgical specimen measured 3 by 2.5 by 1 centimeter. It was soft, elastic, and reddish-brown. On section, a cyst 1 centimeter in diameter filled with soft seminecrotic material was seen. The cytology was quite similar to that of Case 1; however, the tissue showed better organization into acini, a thicker capsule, better delineation of new growth and cystic degeneration. No evidence of malignant change was seen. The microscopic diagnosis was adenoma of parotid gland with cystic degeneration.

CASE 3. F. L., a 37 year old white male, was admitted for treatment of a tumor of the left preauricular region. It had been present for 20 years, gradually increasing in size. An unsuccessful surgical excision had been attempted 5 years previously. Examination showed a firm nodular tumor the size of a "lemon" involving the left parotid gland and adherent to the overlying structures. The clinical diagnosis was mixed tumor of the parotid gland. At operation, a mass 3 by 3 by 2.5 centimeters, including part of the parotid gland, was excised.

On pathologic examination the tumor was firm, smooth, reddish-brown, and almost completely encapsulated. The cut surface was finely cystic and contained much blood. The histologic sections showed no normal parotid gland. Instead there was a dense fibrous stroma supporting numerous interweaving and communicating thick-walled blood vessels of variable size. The vessels showed much evidence of proliferation and were encroaching upon skeletal muscle. Despite the abundant growth of vascular tissue, there was no suggestion of malignancy. The diagnosis was hemangioma of the parotid gland (Fig. 2).

CASE 4. E. E., an 11 month old white female infant, was brought to the hospital because of a mass at the angle of the mandible on the right side. This had been growing slowly since it was first noticed at the age of 2 months. Several x-ray treatments had been ineffectual in stopping the growth. Examination showed a soft cystic tumor mass involving the entire right side of the upper neck and jaw. At operation, the mass was found to be adherent to the surrounding structures and covered with large tortuous veins. It involved the right submaxillary gland and extended posteriorly to the bifurcation of

Fig. 1. M. C., 25484. Adenoma of parotid gland. Eosin and methylene blue stain. ×162.

Fig. 2. F. L., 39987. Hemangioma of parotid gland. Phosphotungstic acid and hematoxylin stain. ×70.

the carotid artery. The mass was dissected free and removed together with the submaxillary gland.

The surgical specimen was an irregular, firm mass 2 by 3 by 3.5 centimeters. It was made up of dark red tissue with a firm pinkish-tan mass representing the submaxillary gland at one end. Histologic sections showed a plexiform mass of capillary blood vessels in the salivary gland and surrounding tissues. The diagnosis was hemangioma (Fig. 3).

CASE 5. R. E., a 26 year old white male, had noted a swelling at the angle of the left side of the jaw since childhood. It had varied in size, was occasionally tender and sensitive. Lately it had so increased in size as to interfere with shaving. Examination showed a soft mass 6.5 centimeters in diameter. At operation a multilocular, dark gray cyst was found lying beneath the platysma muscle on the left side and closely attached to the submaxillary gland.

The surgical specimen measured 4 by 4 by 3.8 centimeters. A partially collapsed, multiloculated cystic mass was attached to a fragment of normal salivary gland. Microscopic examination showed, in addition to normal salivary gland, several small cysts with thin fibrous, endothelium-lined walls. Diagnosis was cavernous lymphangioma (Fig. 4).

CASE 6. A. J. G., a 40 year old white male, noted a small painless swelling in the right side of the neck under the jaw, progressively enlarging for 6 months before hospital admission. On physical examination there was a discrete, nontender, resilient tumor, the size of a "walnut" in the right submaxillary region. An x-ray film showed no opacity. At operation the mass was found to be encapsulated, firmly adherent to the submaxillary gland at its inferior margin. It was easily shelled out when the capsule was incised.

The surgical specimen was ovoid, lobulated, encapsulated, firm, and yellowish-brown. It measured 4 by 3.5 by 2.5 centimeters. On section, the cut surfaces bulged, and had a translucent cast with foci of hemorrhage in a yellowish-gray parenchyma. Microscopic study showed a compact mass of elongated smooth muscle fibers either lying in a parallel arrangement or forming an interwoven matrix. The nuclei were ovoid and plump without any evidence of increased cellular activity. There were fairly abundant fibrous strands and collagen. Special stains revealed most of the elements in the new growth to be of smooth muscle origin. The diagnosis was leiomyoma of submaxillary gland (Fig. 5).

Fig. 3. K. E., 10068. Hemangioma of submaxillary gland. Hematoxylin and eosin stain. ×80.

Fig. 4. R. E., 23906. Cavernous lymphangioma of submaxillary gland. Eosin and methylene blue stain, ×45.

CASE 7. T. W., a 14 year old white boy, was seen because of a painless, slowly growing tumor in front of the left ear of 6 years' duration. The mass was firm, smooth, slightly tender, and fixed. It was about 3.5 centimeters in diameter. The preoperative diagnosis was mixed tumor of the parotid gland. He was operated upon with removal of a necrotic, dark brown tumor.

The mass weighed approximately 4 grams. In it there were many areas of soft to firm, pale gray to dark red tissue. Histologically, the tissue was made up of compactly arranged, elongated cells of uniform size, shape, and staining reaction. These cells had clear fusiform nuclei. It was impossible to make out the ends of the fibers. This neoplastic tissue formed its own stroma. Many foci of calcification and loculated hemorrhages were found. The diagnosis was perineurial fibroma (Fig. 6).

CASE 8. C. F. N., a 69 year old physician, was first seen on July 20, 1939 with a painless swelling in the left parotid region of 2 months' duration. At operation surgical removal of a well encapsulated, roughly ovoid tumor 3 by 2 by 1.5 centimeters was done. This tumor proved microscopically to be a papillary adenocystoma lymphomatosum. One and a half years later he was readmitted to the hospital with a similar swelling in the right parotid gland of 3 months' duration. Excision of this tissue revealed a spherical cystic mass 3 centimeters in diameter which shelled out of the right parotid gland. During removal it ruptured and mucinous material escaped.

The surgical specimen contained salivary gland in addition to a soft, reddish-gray mass measuring 3.2 centimeters in diameter. Section showed a firm, bulging, homogeneous pale red and gray surface with flecks of sticky mucin. Microscopic study showed portions of normal parotid gland. The rest of the specimen was made up of thick papillary projections composed of dense lymphoid tissue surmounted by ciliated, mucin-laden, tall columnar epithelium. This tumor was similar to that removed from the left parotid region a year and a half previously. Diagnosis was again papillary adenocystoma lymphomatosum.

Before the operation on the left side, the clinical diagnosis was mixed tumor of the parotid gland. However, before the one on the right, the tumor was suspected to be similar to the former one.

CASE 9. M. F., a 72 year old, white male, had noticed a slowly enlarging lump in front of the left

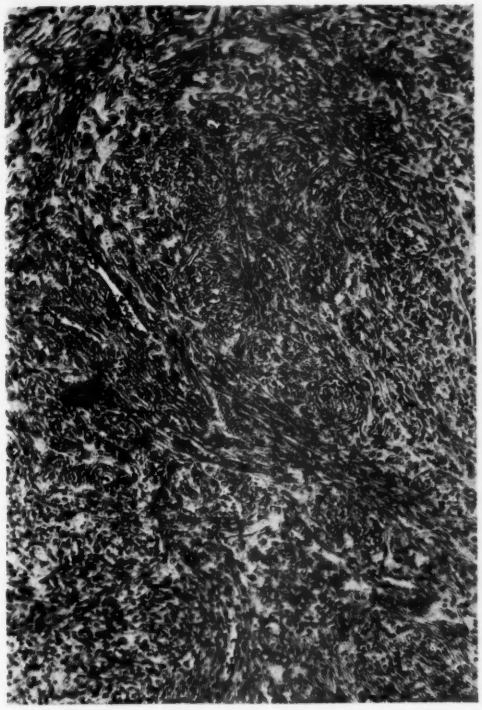

Fig. 5. A. J. G., S-40-520. Leiomyoma of parotid gland. Phosphotungstic acid and hematoxylin stain, ×162.

Fig. 6. T. W., 31399. Perineurial fibroma of parotid gland. Hematoxylin and eosin stain, ×120.

ear for 3 years. This was a moderately soft, nontender, slightly movable mass, 1½ inches in diameter. The cystic tumor, located in the superficial portion of the left parotid gland, was surgically excised. A small amount of yellow, purulent-appearing fluid escaped when the cyst was broken in one place during removal.

Pathological examination showed a soft, fleshy, encapsulated cyst containing friable pink tissue. Microscopically, the tumor was similar to that in Case 8. The diagnosis was papillary adenocystoma lymphomatosum (Fig. 7).

CASE 10. A. J. S., a 45 year old white woman, was first seen November 9, 1933 because of a gradually enlarging mass on the right side of the face which was first noted following the extraction of a molar tooth 6 weeks previously. On examination, the right parotid gland presented a rounded tumor just below the zygomatic arch and anterior to the auditory canal. The tumor was the size of a "walnut." Intraorally there was a tense, round, firm bulging tumor on the medial aspect of the ascending ramus of the mandible. The clinical diagnosis was mixed tumor of the parotid gland. This was later changed to carcinoma simplex on the basis of an aspiration biopsy. Despite temporary remission as a result of radiation therapy, the patient died on July 19, 1938. At this time the local neoplasm had ulcerated, and there was invasion of the right naris.

At autopsy the soft, friable, reddish-gray tumor was found to have penetrated the bones of the base of the skull and extended to the right temporal lobe of the brain; it had eroded the right orbit posteriorly, the right maxillary sinus and zygomatic arch; and it had destroyed the ethmoid bone and sella turcica. The origin was still thought to be the right parotid gland.

Cytologically the neoplasm consisted of closely packed, elongated cells, focally arranged and isolated by necrotic tissue. The cells blended with each other, had plump oval nuclei, and were assembled in interlocking fascicles. Many bizarre nuclear forms and asymmetrical mitoses were seen. No cross striations were found, but the malignant cells took the usual stains for muscle. The final diagnosis was leiomyosarcoma of the parotid gland (Fig. 8).

CASE 11. W. B., a 60 year old, white male had noted a painless, gradually enlarging mass in front of the right ear for 8 months. A smaller nodule was present in the neck. Examination showed a hard,

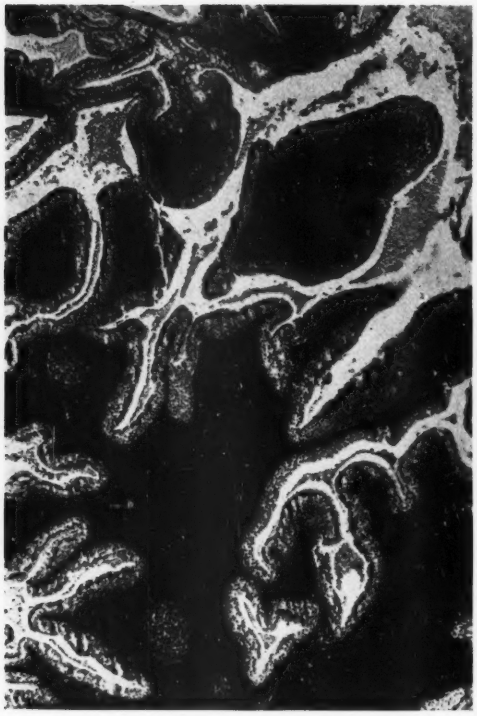

Fig. 7. M. F., 35006. Papillary adenocystoma lymphomatosum. Hematoxylin and eosin stain, ×72.

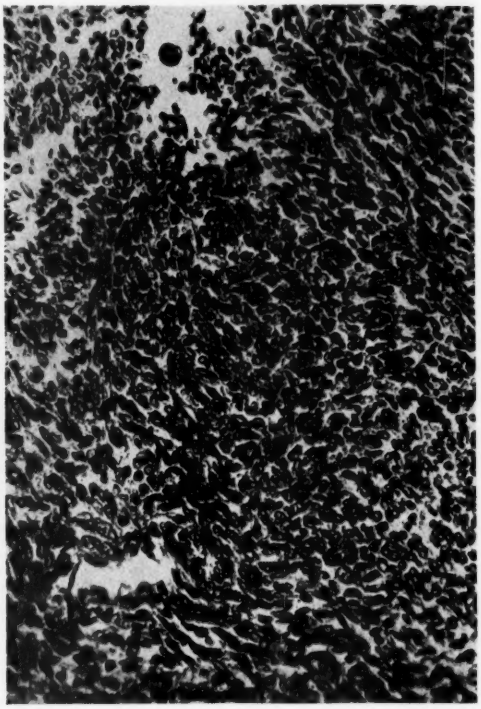

Fig. 8. A. J. S., 38-A-82. Leiomyosarcoma of parotid gland. Phosphotungstic acid and hematoxylin stain, ×475.

ovoid, slightly movable tumor 3 by 2 by 2 centimeters in the region of the right parotid gland, and a smaller, roughly spherical mass 1.5 centimeters in diameter lying beneath it. Although the primary choice was parotid tumor a clinical diagnosis of lymphoma was considered because of the enlarged node in the left side of the neck, and a palpable node in the groin. At operation, two tumors were excised from the right parotid gland. The larger measured 5 by 4 by 3 centimeters, and occupied the middle and upper portions of the gland; the smaller was in the lower half of the gland and measured 2.5 by 2 by 2 centimeters. There was no definite plane of cleavage.

Examination of the specimens showed normal salivary gland incorporating firm, pale gray, rubbery, well vascularized, homogeneous tumor tissue. Histologic study showed some residual parotid gland, but the significant change was the extensive replacement by mature and immature lymphoid elements. The widespread invasion by young and old lymphocytes with many cells in mitosis indicated a diagnosis of lymphosarcoma (Fig. 9).

CASE 12. O. H., a 68 year old white woman, was first seen because of a mass at the right angle of the jaw closely attached to the lower portion of the parotid gland. It had been painful on occasions. The mass was first noted 5 months previously after recovery from a respiratory infection. Physical examination revealed a fixed, nontender, oval mass, 12 by 9 by 8 centimeters lying beneath the angle of the jaw on the right side. Intraoral examination was negative. A clinical diagnosis of lymphoma or metastatic tumor was made. Biopsy was performed. At operation the new growth lay within the right parotid gland and there was no obvious line of demarcation. Gross and microscopic study substantiated the clinical impression of lymphoma. The final diagnosis was malignant lymphocytoma. No evidence of recurrence following radiation therapy was reported in a follow-up examination 2 years later.

CASE 13. C. B., a 51 year old white woman, was seen because of a tumor near the angle of the right side of the jaw which had been present for 3 months and had recently been increasing in size. On examination the mass was fixed to the tissues, lay in or near the submaxillary gland, and was described as being the size of a "hen's egg." Some enlarged cervical nodes were found in the supraclavicular

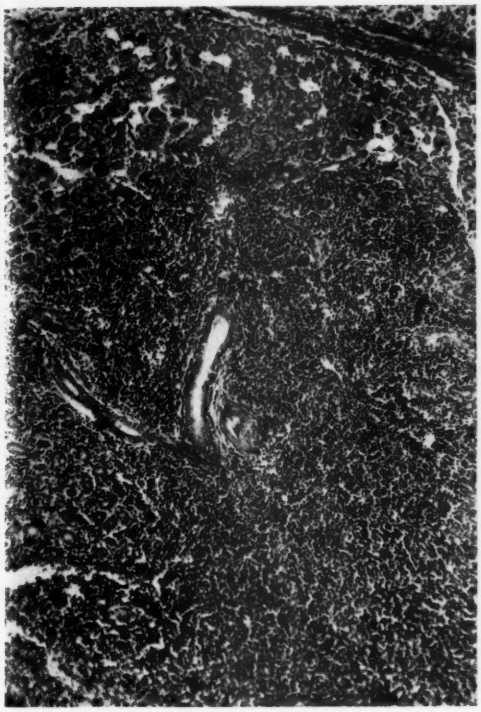

Fig. 9. Lymphosarcoma of parotid gland. Eosin and methylene blue stain, ×90.

region, anterior to the sternocleidomastoid muscle. Clinical impression was malignant tumor of the submaxillary gland or a primary bony neoplasm arising in the mandible. At operation a firm, reddish-gray neoplasm 4 by 4 by 3 centimeters was shelled out of the right submaxillary gland. The surgeon's diagnosis was mixed tumor.

A pathologic diagnosis of atypical Hodgkin's disease was made on the basis of neoplastic destruction of normal submaxillary gland, pleomorphism, abundance of reticulum cells, young and old lymphocytes and eosinophils; fibrosis; necrosis; and the presence of large multinucleated giant cells suggestive of the Reed-Sternberg type (Fig. 10).

Follow up 4½ years later revealed the patient to be still living.

DISCUSSION

Adenomas of the salivary glands have been reported by several authors. McFarland (5) presented a critical review of a large number of cases reported as adenoma of salivary gland, and added 1 case of his own.

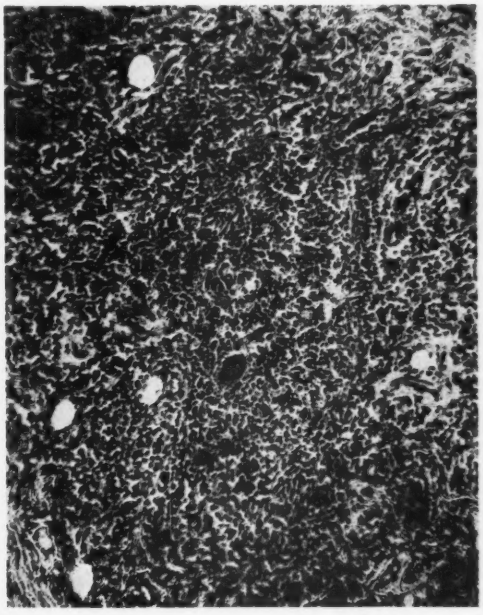

Fig. 10. C. B., 36783. A typical Hodgkin's disease of submaxillary gland. Phosphotungstic acid and hematoxylin stain, ×210.

He regarded most of the so-called adenomas as variants of the mixed tumor showing a preponderance of glandular tissue, and questioned the evidence in favor of their originating from salivary gland *per se*. Harris (2) described the morphology of 1 case in detail. He concluded that the tumor in his case arose from duct epithelium. This view is an acceptable interpretation of the first 2 cases presented here, since the histologic appearance of the neoplastic cells in both cases is suggestive of the duct epithelium of salivary glands. Additional evidence of the adenomatous nature of the tumors is the fact that both were encapsulated. Clinical information regarding these cases is inadequate, and no diagnostic criteria for recognition of these tumors preoperatively can be deduced.

Salivary gland angiomas have been encountered infrequently. McFarland (6) mentions 2 of unspecified type. Both were seen in infants. In the present group, 2 were of blood vessel type and 1 of lymphatic derivation. In 2 the duration was from childhood,

and the third occurred in an infant. Clinically, the long duration of the tumor, while not specific for angioma, would tend to exclude the diagnosis of mixed tumor. Furstenberg indicates that the appearance of mixed tumors of the salivary gland is most common in the third or fourth decades. At the time of operation the unusual bleeding of the hemangiomas was suggestive of the type of growth.

Perineurial fibroma of the salivary glands is seen rarely. McFarland (6) reported 2 cases, 1 with recurrence. Its origin is from the main trunk or a branch of the seventh nerve. Thus it arises within but not actually from the parotid gland. Developing in childhood and growing slowly, it usually results in the signs of tumor only. Occasionally there may be twinges of pain. The diagnosis may be surmised clinically, but is actually based upon the microscopic picture. Some may undergo malignant change. After the material for this paper was gathered, a 2 year old child was operated upon by Dr. R. B. Cattell because of a large mass involving the right parotid gland. This proved to be a perineurial fibrosarcoma of low grade malignancy.

Lately there has been much interest in that bizarre tumor of the salivary gland, the papillary adenocystoma lymphomatosum. In 1937 Harris (3) described the entity and reviewed the literature. Joyce and associates described a series of 4, one of which showed an early adenocarcinoma and another a squamous cell carcinoma. The characteristics of this new growth have been elaborated so clearly that further discussion is unnecessary. Case 8 is unusual in that the tumor occurred bilaterally. We believe that this tumor is not an uncommon one. In the past year we have encountered 6 additional examples, including another case of bilateral tumors.

Leiomyoma of a salivary gland is so rare as to justify reporting it alone. In the case described it arose in the right submaxillary gland. It was encapsulated and easily excised. The histogenesis is unknown. None of the more extensive works has included this particular histologic form. Its clinical diagnosis would be improbable.

The malignant counterpart of the leiomyoma proved to be a confusing neoplasm, and the diagnosis was not established until an autopsy had been performed. An incorrect structural diagnosis had been made on the basis of an aspiration biopsy. The origin of such sarcoma in the parotid gland is obscure; it could conceivably arise in the walls of blood vessels. The response to radiation therapy was unsatisfactory, and the clinical course corresponded to that of a carcinoma. Cytologic study showed a typical malignant smooth muscle neoplasm. Special stains were confirmatory. There are no criteria other than microscopic appearance for the diagnosis of this tumor.

Malignant lymphoid neoplasms may arise in the salivary glands. All 3 of the cases reported here were primary on the right side. Two originated in the parotid and 1 in the submaxillary gland. They were characterized by rapid enlargement in the fifth or sixth decades of life. In 1 case a clinical diagnosis of lymphoma was entertained because of associated cervical adenopathy. The diagnosis in all cases was established by microscopic study. Three types are represented—lymphosarcoma, malignant lymphocytoma, and atypical Hodgkin's disease.

SUMMARY

Thirteen uncommon tumors of the salivary glands have been presented: adenoma, 2 cases; hemangioma, 2; lymphangioma, 1; perineurial fibroma, 1; papillary adenocystoma lymphomatosum, 2; leiomyoma, 1; leiomyosarcoma, 1; lymphomas, 3 cases—lymphosarcoma, malignant lymphocytoma, and atypical Hodgkin's disease.

An attempt has been made to give certain criteria which may aid in their clinical diagnosis.

Although the greatest number of neoplasms arising in the salivary glands are mixed tumors, it should be remembered that other types of tumors may also arise in them.

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STIMULATION OF OVARIAN FUNCTION AND INDUCTION OF PREGNANCY THROUGH INTRAVAGINAL IMPLANTATION OF ESTROGEN PELLETS

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THE problem of amenorrhea plays a very significant role in the treatment of sterility. When ovarian function is at a standstill ovulation does not occur, the building up of the uterine mucosa is inhibited and, as a result, it becomes impossible for fertilization to take place. Since the discovery of the central regulation of ovarian function through the gonadotropic hormone of the anterior pituitary lobe (12, 13, 28) we distinguish between several types of amenorrhea (20): (a) prolanogenic or hypophyseal, (b) estrogenic, (c) progestogenic, (d) hypothalamic (4).

In groups b and c it is necessary to differentiate between ahormonal or oligohormonal and polyhormonal types (15). In the ahormonal and oligohormonal conditions, comprising the majority of the cases, amenorrhea is caused by the absence or the insufficient production of the ovarian hormones. With complete cessation of ovarian function (ahormonal condition) an excess of follicle-stimulating hormone is produced in the anterior pituitary lobe and is excreted in the urine (14). In a castrated woman the follicle stimulating hormone content of the urine rises from 10 to 100 mouse units per litre as early as 14 days after the operation, and the same occurs physiologically at the climacterium (14). Low excretion of estrogens combined with deficient excretion of follicle stimulating hormone indicates hypophyseal amenorrhea, combined with increased excretion of follicle stimulating hormone ovarian amenorrhea, and with normal excretion of follicle stimulating hormone hypothalamic amenorrhea (4). The polyhormonal conditions depend on a disturbance in the ovarian function leading to the persistence of the follicles or of the corpus luteum with hypersecretion of estradiol and progesterone, respectively.

Amenorrhea may be the symptom of a general disease such as diabetes, blood disease, hyperthyroidism or hypothyroidism; or it may be the result of psychic or climactic factors. In such cases one must attempt to cure the amenorrhea through the elimination of the underlying disease. Actually, however, many amenorrheas are of endocrine origin, reflecting a disturbance in the pituitary-ovarian relationship. We are employing a therapy of substitution when we first bring about proliferation of the uterine mucosa in an amenorrhoic patient with the aid of estrogenic hormone, then induce mucosal function through the administration of progesterone, and finally bring on a true menstruation by withdrawal of the hormones. On the other hand, when we attempt to stimulate the ovarian function with gonadotropic hormone, we are employing a hormonotropic stimulation therapy (Zondek). The final object of all treatment must be to initiate rhythmic function of the gonadotropic hormone in the anterior pituitary lobe.

The anterior pituitary gland is the motor of sexual function (12, 13, 28). Under the influence of gonadotropin, estradiol is produced in the follicular theca cells, and this hormone exerts a reciprocal effect on the anterior pituitary function. In 1931, the senior author summarized (18) his investigations as follows:

Estrogenic hormone acts both as a stimulator and an inhibitor of the function of the anterior pituitary lobe, with the result that the estrogenic hormone, produced in the ovary under the influence of the anterior pituitary, has a regulating effect on its producer. The motor of the sexual function is, thus, regulated by the substance it produces, since small doses of estrogens stimulate while large doses inhibit it.

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EXPERIMENTAL STUDIES

Experimental studies of the senior author have demonstrated (22, 23) that uninterrupted treatment with large doses of estrogens is capable of inhibiting the function of the anterior pituitary lobe, actually affecting certain specific functions, one of the most sensitive of which is the gonadotropic function, followed, in that order, by inhibited production of growth hormone. If rats or fowl are treated for several months with estrogens they develop into eunuchoid dwarfs. Body growth is inhibited in such animals by as much as 60 per cent, and the development of ovaries and testes by 95 per cent. Atrophy of the sex glands, absence of follicular maturation and of corpus luteum formation, and inhibition of spermatogenesis are all complete. Estrogenic hormone may thus induce partial biological resection of the anterior pituitary, since the gonadotropic function and the production of growth hormone are thereby inhibited, while the other hormonotropic functions are only slightly or not at all affected. Whereas inhibition of the anterior pituitary by means of large doses of estrogens is easy to achieve, experimental stimulation is extremely difficult and may be carried out only with small doses of hormone. It is important that the hormone be constantly absorbed and that it exert a continuous effect on the anterior pituitary, a condition which was found not to be fulfilled when hormone was injected, since in this case over-rapid resorption was followed by excessively rapid enzymatic inactivation in the liver (16, 17, 29, 30). Deanesly and Parkes (1, 2) demonstrated that the desired continuous resorption was achieved when hormone pellets were administered, as only 1 to 5 per cent was resorbed daily when this method was employed. Stimulation of the anterior pituitary was obtained in rats and rabbits with the aid of the implantation technique (25, 26). The production of growth hormone, gonadotropic hormone, lactotropic hormone, and in other experiments, of thyreotropic hormone were all stimulated thereby. To begin with the last mentioned effect, it was thus possible to imitate the human syndrome of Graves' disease in laboratory animals. The animals exhibited loss of weight, nervous irritability, increased basal metabolism, typical electrocardiographic changes, and extreme exophthalmos. Furthermore, giant animals were produced, with enormously enlarged mammary glands, markedly increased milk secretion, and ovarian hypertrophy with marked development of lutein tissue. Thus, it proved possible through continued exposure to small quantities of estrogenic hormone to stimulate the secretion of various hormonotropic factors of the anterior pituitary lobe.

CLINICAL STUDIES

On the basis of the experimental results, we attempted to stimulate the function of the anterior pituitary lobe by means of uninterrupted action of estrogenic hormone in man, as well. Here too, after attempts at injection had proved unsatisfactory, the implantation of pellets appeared promising. We then tried the implantation of pellets in the customary manner, subcutaneously or intramuscularly on the upper thigh or on the abdominal wall, but we were dissatisfied with the results thus obtained. The efficacy of this method varied from case to case, probably because the pellets implanted in subcutaneous tissue were readily encapsulated and were thus rendered inactive due to the fibrous growth, whose intensity varies in different people. We then demonstrated experimentally that the activity of estrogenic hormone was greatly increased when the hormone was injected near its target organ, i.e., in the vaginal submucosa. The dose of estrone required to elicit estrus by the intravaginal route is only a fifth of the subcutaneous and intramuscular doses required. Therefore, we chose the intravaginal pellet implantation (Zondek) which has the following advantages (27):

a. Absorption is much more constant than in the case of subcutaneous implantation, probably because the blood supply of the vagina is superior to that of the subcutaneous tissue.

b. The effective activity of pellets implanted submucosally in the vagina is about 5 times that of pellets implanted subcutaneously.

c. Expulsion of pellets, such as sometimes occurs following subcutaneous implantation, is rare.

Implantation may be successfully done in the posterior wall of the vagina, about 2 centimeters beyond the vaginal orifice. Following infiltration with 0.5 per cent novocain, a small incision is made in the mucosa, and, with the aid of a forceps, this is very easily converted into a cavity in the submucosa, in which several pellets may be implanted at different sites. Fuller details of the technique may be found in the original paper (27).

Dosage. The question of the amount of hormone to be implanted is of decisive importance. If the dose is too small the effect is negligible. If it is too large, the resulting stimulation of the uterine mucosa (peripheral effect) has a disturbing influence, leading to unpleasant clinical symptoms such as bleeding, which will be more fully discussed. The dosage must be independently determined in each case. In cases of secondary amenorrhea, we may take as a base line a dose of no more than 30 to 35 milligrams of estrone or estradiol for the first implantation, about 25 milligrams for the second implantation which follows after an interval of about 3 to 6 months, and the same dose for a third implantation, several months later. In primary amenorrhea, the initial dose may be 35 to 50 milligrams maximum, and implantations of 30 to 40 milligrams may follow.

Preparation of the pellets. The pellets were produced as follows: 10 to 25 milligrams of hormone (estrone or estradiol), without the addition of any binding substance, were pressed by hand into a brass tube 2.5 millimeters in diameter, with the aid of a brass piston. The pellets thus produced had a diameter of 2.5 millimeters, and were 1 to 3 millimeters thick. The pellets were sterilized by dry heat for 24 hours at 100 degrees C.

Effect of the pellets. The constant resorption of estrogenic hormone from the pellets provides the body with a protracted hormonal stimulus which has the following effects:

Central effect, i.e., stimulation of the gonadotropic function of the anterior pituitary lobe with consecutive production of the ovarian hormones.

Peripheral effects: (a) stimulation of uterine growth and of proliferation of the uterine mucosa, (b) probable stimulation of the ovary.

Stimulation of the production of gonadotropins in the anterior pituitary lobe (follicle stimulating hormone and luteinizing hormone) leads to the production of sex hormones in the ovary, specifically of estradiol in the theca cells and of progesterone in the granulosa cells (central effect). These substances, in turn, stimulate the uterine mucosa, leading to proliferation of and secretion by the mucous membrane, thus preparing it for the nidation of the fertilized ovum. Moreover, the pellet containing estrogens causes a direct (peripheral) stimulation of the uterus, of its vegetative function, increased uterine growth as well as of its generative function, proliferation of the uterine mucosa. Certain experimental studies suggest that the ovary may also be stimulated by the estrogenic hormone. Pencharz, working with infantile hypophysectomized rats, implanted diethylstilbestrol and followed this by treatment with chorionic gonadotropin, thereby not only inhibiting the atrophy of the ovary, but actually obtaining considerable increase in weight, with enlargement of the follicles and the corpora lutea. Similar results obtained by other authors (3, 8, 9, 11) suggest the conclusion that the estrogenic hormone renders the ovary sensitive to the influence of hypophyseal gonadotropin. It is quite possible that this effect is implicated in our cases as well, and that the restoration of the cycle may perhaps be favored by it, in that the central effect of gonadotropic stimulation is combined with the peripheral effect on the ovary, leading to further sensitization of the ovary to gonadotropin.

Too strong an induction of the peripheral effect on the uterine mucosa may result in hyperproliferation (glandular cystic hyperplasia), which is sometimes known to provoke bleedings, often of a severe nature. We have observed this undesirable by-effect, and have several times been obliged to perform curettage in cases of protracted, or occasionally of violent bleeding. An attempt should first be made to check the bleeding through the administration of 10 milligrams of progesterone daily for 5 days, and only if this proves unsuccessful, should curettage be performed. Following curettage the cycle is sometimes spontaneously initiated, but in other cases amen-

orrhea recurs, necessitating a second implantation. The disagreeable by-effects should not discourage further implantations, since stimulation of the anterior pituitary must be the constant aim. We have arrived at this point of view on the basis of the following observations. Repeated intravaginal implantation was capable of inducing not only uterine growth producing an organ of normal size, but also restoring ovarian function and ultimately pregnancy in women who had been amenorrhoic for years and had exhibited symptoms of complete inhibition of ovarian function, such as very small, atrophic uterus, atrophic mucosa, complete absence of estrogenic reaction in vaginal smears, increased secretion of follicle stimulating hormone (110 mouse units or more per litre urine), symptoms of vasomotor insufficiency, etc. We have been able in recent years almost completely to avoid the bleedings induced by implantation, since we have determined the proper dosage. Bleedings were brought on by the implantation of 50 to 75 milligrams of estradiol, doses which we have since rejected as excessive, since we now consider 40 milligrams to be the maximal permissible dose.

Success of the treatment. Sixty-two women were treated for amenorrhea by intravaginal implantation. The pellets consisted of either estradiol, or, in most cases, of estrone. Seven of the patients suffered from primary amenorrhea, i.e., they had never yet menstruated; and 55 of them had secondary amenorrhea of 2 to 10 years' duration. Of these 62 patients, 52 responded with bleedings, and 38 of them reported several cyclic bleedings following a single implantation; while 26 had regular bleedings up to 12 months. In 12 cases the cycle was completely established, and 8 of these women became pregnant.

Fifty-four of the 62 patients were married, and since 8 of the patients became pregnant the treatment was entirely successful in 14.8 per cent of the cases. It should, indeed, be emphasized that we did not consider any other possible causes of sterility, as we were particularly concerned with the initiation of ovarian function and ovulation, which is the prerequisite condition for fertilization. Some of our patients may have had occluded tubes, or other causes for sterility, so that our 14.8 per cent would represent the minimal number of successful treatments.

In this study we will not describe in detail all of the 62 cases in which patients were treated by intravaginal implantation, but only those which culminated in pregnancy.

The following case demonstrates the disadvantages of the method, i.e., the marked local stimulation of the uterine mucosa with severe bleeding. It should be noted, however, that these accessory phenomena have been avoided in recent years, since the dosage has been more carefully worked out. As may be seen in the case history, we implanted 50 milligrams of estrone, a dose which we would now consider excessive since we do not now exceed doses of 25 to 30 milligrams in cases of secondary amenorrhea. In spite of the bleeding, which is certainly to be regarded as an unpleasant accessory phenomenon, we successfully induced ovarian function and reinitiated the cycle in a woman amenorrhoic for 6 years.

Mrs. S., aged 29 years, childless after 9 years of married life, was completely amenorrhoic for the past 6 years and suffered from symptoms of vasomotor insufficiency. The uterus was atrophic, the mucosa very thin, containing only a few scattered glands in a resting condition. Examination of a vaginal smear revealed estrogenic insufficiency. On March 16, 1942 intravaginal implantation of 50 milligrams of estrone was done. Fifty-two days later the patient bled for 2 days, and a severe bleeding, necessitating curettage, followed 23 days thereafter. Strip curettage revealed marked glandular cystic hyperplasia of the mucosa. Amenorrhea returned following the curettage.

A second intravaginal implantation of 50 milligrams of estrone was made in January, 1943. After an interval of 4 months, severe bleeding again necessitated curettage. Marked glandular hyperplasia was again observed in the mucosa. However, after this curettage, menstruations lasting for 4 to 5 days set in at intervals of 28 days, and the patient was completely cured of her 6 years' amenorrhea.

PREGNANCIES

In 8 cases implantation induced not only bleedings but regular cycles, with ovulation, as demonstrated by the fact that the patients became pregnant. We treated only such patients as appeared to us clinically severe, and with unpromising prognosis. All our patients exhibited marked degeneration of the genital organs; details of the symptoms are presented

below. All had already been unsuccessfully treated for extended periods of time. One patient, a 26 year old woman, had menstruated only a few times in her life; in other words she actually represented a case of primary amenorrhea. The 7 others were cases of secondary amenorrhea of between 2 and 5 years' duration. Sterility had lasted for 3 to 7 years, with an average period of 4.6 years. The following are detailed histories of the cases:

Primary Amenorrhea

CASE 1. Th. G., a 26 year old woman, childless after 3 years of marriage, first menstruated at the age of 15. Slight bleedings followed at intervals of several months, for 2 years. Then menstruation ceased. The patient suffered from nervousness, sometimes amounting to depression, actually brought on by a feeling of sexual inferiority.

Examination revealed an atrophic vagina and an extremely infantile uterus, with complete atrophy of the uterine mucosa. Total estrogenic deficiency was revealed by vaginal smear and by abnormally high urinary excretion of follicle stimulating hormone (333 mouse units per litre). Basal metabolism was +7 per cent. The case appeared almost hopeless due to the marked atrophy of the genitals. Repeated implantation was nevertheless undertaken in the hope that this treatment might induce uterine growth and might perhaps reinitiate ovarian function.

January 20, 1941, intravaginal implantation of 50 milligrams of estradiol was done. Slight bleeding occurred 42 days thereafter. Strip curettage showed that the mucosa had already developed to a certain extent, corresponding approximately to the 12th to the 14th day of the cycle. The follicle stimulating hormone litre units per litre of the urine had fallen from 333 to 86 mouse units per litre. On May 13, 1941, i.e., 112 days after implantation, bleeding again occurred, and 4 cyclic bleedings followed at intervals of 28 days. The significant growth of the uterus, which now appeared almost normal in size, was striking. The previously somewhat atrophic breasts were greatly enlarged and painful. After ovarian function had continued rhythmically for 4 months with progestative development of the mucosa indicating ovulation (proved by strip curettage), an amenorrhoic period of 3 months' duration followed, whereupon an additional intravaginal implantation of 40 milligrams of estradiol was administered. Two months later the cycle was reinitiated and 12 regular bleedings occurred. In February, 1943 the patient became pregnant and a normal birth followed. The cycle remained normal after the patient gave birth, and she became pregnant a second and a third time.

In this apparently almost hopeless case, repeated implantation had resulted in complete functional success.

Secondary Amenorrhea

CASE 2. Ch. W., a 34 year old woman, childless after 4 years of marriage first menstruated at the age of 16, followed by irregular menstruations at intervals of 4 to 6 months. Amenorrhea had been complete for the past 2 years. If the bleedings induced by hormone injections are included in the calculation, the patient must be considered to have been amenorrhoic for at least 6 years.

The sex organs were markedly underdeveloped, the uterus being small and the uterine mucosa very atrophic, thin, containing only a few glands. The breasts were very underdeveloped. Conspicuous symptoms of vasomotor insufficiency were noted, such as flushes and attacks of perspiration, irritability, and insomnia.

September 1, 1941, 50 milligrams of estradiol were implanted intravaginally. Several weeks later the patient felt a distinct subjective improvement: the flushes diminished in severity, the nervous irritability subsided, and her breasts had developed to a certain extent. The patient noted particularly that the hitherto constant dryness of the vagina during cohabitation no longer persisted. Eighty-eight days after implantation a 10 day bleeding period set in (November 27, 1941) and bleedings recurred in December, 1941, and in January and February, 1942. Since no bleedings occurred in March and April, a second implantation of 30 milligrams was administered. Two months later bleeding recurred and the patient became pregnant during the following month. Pregnancy and birth were normal.

CASE 3. L. Z., 30 year old woman, childless after 6 years of marriage, first menstruated at 13 years. Menstruation was regular until 2 years previous to examination, since when no bleedings had occurred. During this period the patient had been suffering from severe nervous symptoms, headaches, and depressive states.

Examination revealed a somewhat atrophic vagina, and no estrogenic activity was revealed by vaginal smear. The uterus was very atrophic, with a thin mucosa containing only a few glands in the postmenstrual stage.

July 7, 1941, 25 milligrams of estradiol were implanted intravaginally, but this treatment remained ineffective; whereupon a second intravaginal implantation of 50 milligrams of estradiol was carried out on October 24, 1941. In consequence, a bleeding was induced which began on January 1, 1942 and became progressively more severe, so that curettage became necessary by the end of the third week, and a very hyperplastic mucosa was removed at this operation. Bleedings recurred in February and March, and these were followed by an amenorrhoic period, necessitating a third intravaginal implantation of 35 milligrams of estradiol in January, 1943. Bleeding was re-established in March, 1943, and normal menstruations followed for 8 months, when, in December, 1943, the patient became pregnant. Birth was normal.

CASE 4. Z. T., 30 year old woman, childless after 6 years of marriage, first menstruated at 14 years, with regular menstruations until 3 years before examination, when complete amenorrhea set in following a spontaneous abortion. Since that time, there has been a marked gain in weight, associated with headaches and dizziness.

The uterus was atrophic, the corpus small. The uterine mucosa was very thin, with small glands corresponding to the postmenstruum.

March 1, 1942 intravaginal implantation of 25 milligrams of estradiol was done. The first bleeding began 83 days after implantation, on May 22, 1942. Bleedings recurred on July 26, August 23, and September 19, 1942, followed by regular menstruations at intervals of 28 days, until the patient became pregnant in February, 1943. Pregnancy and birth were normal.

CASE 5. B. H., 31 year old woman, childless after 5 years of marriage, first menstruated at 15 years. Menstrual periods were very irregular, with intervals of up to 1 year's duration. Complete amenorrhea had been present for the past 4 years. Judging from the course of the disease, amenorrhea must have been of at least 8 years' duration. April 23, 1942, an intravaginal implantation of 35 milligrams of estradiol was done. A severe hemorrhage began 85 days thereafter (July 17, 1943), and lasted for 6 days, during which period blood clots were discharged. Two months of amenorrhea followed, whereupon a second intravaginal implantation of 35 milligrams of estradiol was administered. Normal bleedings occurred on December 10, 1943, and in January, 1944, and pregnancy began 1 month later, but was interrupted by an abortion during the second month. Normal menstruation then recurred. Pregnancy again began in August, 1944, but was again terminated by an abortion in the fourth month.

This case is particularly noteworthy, since the patient was of a markedly virile type, with hairy face, legs, and arms. The clitoris was very enlarged, and the uterus small, with an atrophic mucosa containing few glands. Vaginal smear revealed complete lack of estrogenic action.

CASE 6. A. S., 24 year old woman, childless after 2 years of marriage, first menstruated at 13 years. Irregular menstruations were followed by amenorrhea with very rare bleedings, the last one having occurred 4 years previously. Judging from the case history, the patient must be assumed to have been amenorrhoic for 7 years.

External genitalia were infantile, as was the particularly small uterus with markedly atrophic mucosa.

November 30, 1942, 20 milligrams of estradiol were implanted intravaginally. Since this treatment was ineffective, 35 milligrams of estradiol were again implanted on March 9, 1943. A slight bleeding occurred 3 months later, and this was followed by regular bleedings until the patient became pregnant in August, 1943. The pregnancy was normal. The patient again became pregnant in December, 1944; normal birth.

CASE 7. H. H., 33 year old woman, childless after 10 years of marriage, first menstruated at 14 and continued to menstruate regularly until 5 years before examination, when amenorrhea set in following induced abortion. Patient suffered from severe symptoms of ovarian insufficiency: flushes, dizziness, insomnia, and severe states of depression.

Genitalia were markedly atrophic, the vagina pale, the uterus very hypoplastic and small, 5 centimeters in length (corpus 3 cm.). Vaginal smear revealed lack of estrogenic action. Basal metabolism: +6 per cent.

May 4, 1941, 60 milligrams of estradiol benzoate were implanted intravaginally. The first bleeding began 3 months later, and regular menstruations followed, the patient becoming pregnant as early as December, 1941. Spontaneous abortion during the fourth month of pregnancy, followed by a recurrence of amenorrhea accompanied by the symptoms of ovarian insufficiency. A second implantation of 50 milligrams was therefore administered on August 6, 1942. Bleeding began 80 days later, followed by regular menstruations. Pregnancy again began after 7 months, and this time it ran a normal course.

CASE 8. M. G., 34 year old woman, married for 14 years, had borne 3 children, the last birth having occurred 7 years before examination. Since this date there had been only a few periods, with complete amenorrhea for the past 5 years. During this time the patient gained weight, and suffered from flushes, attacks of perspiration and states of depression.

Uterine examination revealed definite signs of atrophy; mucosa atrophic, thin, and containing only a few glands. Vaginal smear revealed marked lack of estrogenic action.

September 30, 1942, 35 milligrams of estradiol benzoate were implanted intravaginally. The first bleeding began 78 days after implantation (December 17), and the second only after an interval of 3 months (March, 1943). Since then menstruations had occurred regularly, until the patient became pregnant in April, 1944. Pregnancy and birth ran a normal course.

DISCUSSION

Whereas a rational therapy for amenorrhea was formerly impossible, since only desiccated ovarian preparations were available and these contained little if any hormone; during the last 2 decades definite progress has been made, due to the discovery and the production of adequate quantities of sex hormones, which make both substitution and stimulation therapies possible. The use of estrogenic hormone enables us to stimulate the uterus vegetatively (in-

crease in growth), and also to initiate its generative function (uterine mucosa). Progesterone is able to induce secretion by the developed mucosa. The bleeding mechanism of the uterine mucosa is initiated by the fall in hormone titre, probably of the estrogenic hormone. Finally, gonadotropic hormone is capable of stimulating ovarian function. However, successful results with human subjects have hitherto lagged far behind those recorded for experimental animals such as mice and rats. Varying results are probably ascribable to insufficient dosage. In 1935, one of us (Zondek, 21) stated that the clinical dose of gonadotropin is 15,000 rat units; and in fact Rydberg (6, 7) employing this dose, was able clinically to achieve the same effect as in animal experiments, i.e., induction of ovarian function by means of the administration of 15,000 rat units of gonadotropin derived from horse serum (follicle stimulating hormone), followed by 3000 rat units of gonadotropin from pregnancy urine (luteinizing hormone).[1] A disadvantage of this therapeutic procedure is the fact that it yields often a single effect, an unrepeated stimulation of the ovary. The ideal therapy, on the other hand, would be the stimulation of the anterior pituitary lobe, the motor of sexual function, so as to induce the periodic production of gonadotropin. This seems to be feasible, as reported in the present paper, by means of stimulation with estrogenic hormone, which can be made to be secreted continuously from implanted hormone pellets.

A disadvantage of this treatment lies in the fact that the intense stimulation of the uterine mucosa may, on occasion, lead to undesirable hemorrhage, which may, however, be controlled by the administration of progesterone or by curettage. We believe that this accessory effect, which may generally be avoided through judicious choice of the dose of estrogenic hormone, is certainly offset by the possibility of curing women of protracted amenorrhea, of releasing them from their inferiority complex, and of enabling them even to become pregnant. This is particularly obvious in Case 1, a patient who would have been considered hopeless before the discovery of the sex hormones. The fact that it was possible to induce normal uterine growth and ovulation eventually terminating in pregnancy in a young woman suffering from complete atrophy of the genitalia, whose uterus was scarcely palpable, and who had menstruated a few times only in her life, demonstrates the progress brought about by hormone therapy. In another patient (Case 5), that of a woman with frank virile symptoms (greatly enlarged clitoris, hirsutism, atrophy of the uterus and the uterine mucosa, complete lack of estrone), we successfully cured an amenorrhea of 4 years' duration, and eventually enabled the patient to become pregnant.

It should be emphasized that a rather long interval, averaging 78 days, elapses between the implantation and the onset of bleeding. From this point on, 3 types of reaction may occur:

a. The initial bleeding begins after approximately 78 days, and is followed by further cyclic bleedings, i.e., ovarian function is restored to normal.

b. The initial bleeding emanates from a hyperproliferated mucosa, and, in cases where it is excessively prolonged, requires either treatment with progesterone or curettage, following which rhythmic bleedings occur at regular intervals.

c. One or several bleedings are again followed by a period of amenorrhea, in which case implantation must be repeated.

Proper dosage is of paramount importance. Though we have defined already the required dosages, we must point out that these merely represent averages, and that in each case the clinical picture must be taken into consideration in determining the dose.

It might be argued that our successful results are in part no more than coincidental, since amenorrhea is known to clear up spontaneously, and pregnancy may even occur in such patients. However, we have pointed out the fact that the patients we selected for treatment all had very unfavorable prognoses, and had undergone hitherto unsuccessful therapy for years. A fundamental characteristic of all our cases is the frank atrophy of their genital organs, as evidenced by hypoestrinism

[1] In his recent investigations A. Westman c.s. (Acta Endocrin., 1948, 1: 1) reported remarkable results in treating amenorrheic women with his cristalline chorionic gonadotropin (36,000 international units intravenously during 3 days).

(vaginal smear), diminution in size of the uterus, atrophy of the uterine mucosa, increased excretion of follicle stimulating hormone, and the secondary phenomena of vasomotor insufficiency characteristic of the climacterium.

In a former study (24, 31, 32), we demonstrated that it is possible to induce bleeding from the atrophic mucosa of amenorrhoic patients by the injection, on 2 successive days, of 5 milligrams of estrone and 50 milligrams of progesterone[1]. It is also feasible to induce this effect with a single injection when the hormones are administered not in an oily solution but in the form of a precipitation of microcrystals of a specific size (33).

If 3 or 4 bleedings are induced by treatments repeated at intervals of about a month, ovarian function may be restored in a certain number of cases, and rhythmic bleedings ensue. It must therefore be concluded, as already pointed out by A. Westman[2] and G. V. Smith, (10), that the cyclic estrogen-progesterone withdrawal flow plays a physiological role in the cyclic pituitary-ovarian interaction. The present investigation demonstrates that the same effect may also be obtained by continuous stimulation with estrogenic hormone flowing from the pellet reservoir. Apparently, the central stimulation of the gonadotropic function of the anterior pituitary lobe combines with the peripheral stimulation of the ovary, sensitizing the latter to the influence of pituitary gonadotropin. As a result, the central mechanism, that of the anterior pituitary as the motor of sexual function, appears to be reinitiated.

SUMMARY

1. Estrogen pellets were implanted intravaginally in severe cases of amenorrhea with consequent sterility.

2. Intravaginal implantation possesses the following advantages over subcutaneous administration: (a) The effect is more constant, since the connective tissue enveloping the introduced hormone in the vaginal submucosa is much less dense than that in the subcutaneous tissue. (b) The effect is about 5 times as intense. (c) the tablets are seldom expelled.

3. The effects of implantation are manifested in improved vascularization of the vagina, in changes in the vaginal epithelium (cornified cells), in uterine growth, proliferation of the uterine mucosa, uterine bleeding and enlargement of the breasts.

4. The average interval between implantation and the onset of bleeding is 78 days.

5. The cycle may be reinitiated by a single intravaginal implantation, whereby the amenorrhea is relieved. Alternatively, several cyclic bleedings may occur which are again followed by amenorrhea, requiring a second implantation after a certain period, or even a third in obstinate cases. A second implantation is also indicated if no bleeding occurs within 3 to 4 months of the initial implantation. The effect of implantation may be estimated by vaginal smear and by the examination of the uterine mucosa obtained by a diagnostic strip curettage.

6. The dosage, which must vary with the severity of the clinical symptoms, is of paramount importance. Doses may range between 25 and 50 milligrams of estrone or estradiol. Doses higher than 50 milligrams are not to be administered.

7. An unwelcome accessory effect sometimes associated with our treatment is an excessively intense peripheral reaction involving glandular cystic hyperplasia of the uterine mucosa, sometimes accompanied by severe bleeding, requiring treatment with progesterone or, if necessary, with curettage. This accessory effect should not discourage a repetition of implantation employing a smaller dose, should amenorrhea reappear. Moreover, excessive bleeding may be avoided if not more than 30 to 40 milligrams of estrogen be implanted.

8. Mechanism of the effect: Estrogenic hormone leads to central stimulation of the anterior pituitary lobe, whereby the secretion of gonadotropin is induced. Furthermore, a peripheral effect on the ovary is probably also induced, rendering the ovary more sensitive to the influence of gonadotropin.

9. We have carried out intravaginal implantation in 54 married women suffering from

[1] The interval between hormone inoculation and bleeding consists of 2 to 3 days following the 2 day administration of oily solutions of hormones, and of 10 to 12 days following the administration of one injection of hormone microcrystals.

[2] Acta obst. gyn., scand., 1935, 15: 1.

amenorrhea of many years' duration, accompanied by severe secondary changes of the genital organs. Bleeding was induced in 84 per cent of the amenorrhoic patients. In 8 of the treated cases (14.8 per cent) not only was the amenorrhea cured, but pregnancy actually ensued. Since other possible factors leading to sterility were not taken into account, as the amenorrhea was the condition most obviously requiring treatment, it may be that the percentage of successful treatments of sterility ought to be estimated at a higher figure. For implantation only such cases were selected which were prognostically unpromising, and which had previously been under other types of treatment for years without any success. It is worthy of note that 1 of our patients, who had menstruated only a few times in her life and whose genital organs were as undeveloped as before puberty, responded to our treatment with complete initiation of genital function, culminating in pregnancy.

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EDITORIALS

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INTRAEPITHELIAL CARCINOMA (IN SITU) OF THE CERVIX UTERI

IN the absence of complete and specific knowledge of the cause of cancer we obviously cannot prevent its occurrence to any great degree. The second best thing that we can do is to recognize it in its incipiency and perfect our therapy at that early stage. Cancer of the cervix uteri is the malignancy which occurs most frequently in the female pelvis. It is second only to breast carcinoma in frequency of malignancy in women. Hence any decisive blow that can be taken at it will materially reduce the death rate of women from cancer. Since the cervix is essentially a surface organ, it lends itself readily to inspection and biopsy. Thus cervical cancer is an ideal lesion for early detection.

In 1912 Schottländer and Kermauner described cellular changes in the surface epithelium about the periphery of invasive cervical cancer that were identical to the cellular changes in the depth of invasive cancer. They believed that invasive cancer sometimes spread on the surface in this manner. It remained for Schiller, who began his studies in the twenties and continued them into the thirties, to conceive the idea that true cervical cancer might begin as a surface lesion and remain such for a considerable period before entering the invasive stage. To substantiate his belief that these surface lesions were actually cancer, Schiller presented histological evidence that was suggestive if not conclusive. He also published clinical facts which supported his views, such as one recurrence after five years and two recurrences in less than five years after hysterectomy. At the present time there are approximately twenty cases in the literature in which death resulted after treatment of an apparent intraepithelial carcinoma or in which patients presented themselves with advanced cervical cancer several years after a recorded biopsy which showed carcinoma in situ. In some instances a period of as long as twelve years had elapsed between the time the biopsy was taken and clinical cancer appeared. Among these cases are those of Stevenson and Scipiades, Pund, Smith and Pemberton, Schnitz and Benjamin, Knight, Younge, Taylor and Guyer, Scheffey, Galvin and Te Linde.

The last two authors have made a prolonged and intensive study to prove histologically the relationship between carcinoma in situ and invasive cervical cancer. All cervices which had shown noninvasive cancer on biopsy and which were subsequently removed were cut into blocks and many sections made from each block of tissue. Of a total of 75 cases they were able to demonstrate invasive cancer histologically in 55. In 10 cases more intraepithelial

cancer was found in the removed cervix and in the remaining 10 no abnormality was found in the entire cervix, indicating that either all the carcinoma in situ was removed at biopsy or that further carcinoma was missed, in spite of the many sections. From these studies and from clinical data, it would seem that the term intraepithelial cancer or carcinoma in situ should be used to indicate a microscopic picture and that such a microscopic picture found in a biopsy may indicate three possible clinical conditions: (1) a gross invasive cancer, the periphery of which was biopsied. This is the condition originally described by Schottländer and Kermauner; (2) a cervix in which subclinical but microscopic invasive cancer exists; (3) a cervix in which the neoplasm is still strictly intraepithelial.

Hence in each instance in which the pathological report of carcinoma in situ is made, the woman should be examined gynecologically and the gross findings correlated with the microscopic evidence. It is only in this way that a proper decision regarding therapy can be made.

It is interesting that in Pund's cases of intraepithelial cancer the average age was 36.6 years and in Galvin and Te Linde's group 37.1 years. Since the average age of patients with cancer of the cervix in its clinical form is 48 years, it would appear that the noninvasive form of the disease may exist for many years before becoming grossly invasive and clinically apparent. This is simply another way of saying that the symptomatic life of a cervical cancer is a relatively short part of its entire existence.

Since the subject of carcinoma in situ and the cytological diagnosis of cervical cancer have come to the attention of the profession more or less simultaneously the relation of one to the other should be given serious consideration. Although the available data regarding the value of smears in detecting carcinoma in situ are relatively meager compared with the biopsy data, sufficient have been accumulated to indicate that many preinvasive carcinomas may be discovered by the study of cytology smears. The relatively or absolutely normal appearance of the cervix may make the taking of biopsies rather difficult. The smear technique does not present this difficulty. Since histological studies have shown that practically all intraepithelial cancers start at the columnar stratified junction, biopsies should be taken there as well as from any isolated suspicious areas. However, smears may be incorrectly taken as well as biopsies. A smear made by the blind introduction of a swab into the vagina is more apt to lead to a false negative report than a smear taken directly from the cervix. When one considers that the percentage of false negative reports for smears in the presence of gross cervical cancer is in the neighborhood of 10 per cent, the greater likelihood of a false negative in the presence of the small nonulcerating, noninvasive cancer becomes apparent. Two points should be emphasized in relation to cytology: (1) a positive smear should always be confirmed by biopsy before beginning treatment for cancer; (2) one should never rest assured that cancer is not present on the basis of a negative smear if the cervix looks at all suspicious. Biopsy examination of such a cervix should be done and should be repeated, if necessary, before one can be satisfied that no cancer is present.

Concerning the treatment of carcinoma in situ there is rather general agreement that total abdominal hysterectomy should be done. Galvin and Te Linde have reported that 67 patients operated upon from 8 years to 6 months before the report were living and free from evidence of cancer. The operation which they performed was called a "modified Wer-

theim." It consists of removal of the uterus with a centimeter or two of parametrium and a wide vaginal cuff. Lymph gland resection is not done, thus greatly reducing the magnitude of the operation. In the younger individuals an ovary was frequently spared and there were no recurrences among these patients. The authors stress the point that they do not advocate this "modified Wertheim" operation for clinical cervical cancer. There is little doubt that the percentage of cures of carcinoma in situ with irradiation would be high, but it is interesting that Galvin and Te Linde report one death among 8 patients treated by irradiation. This woman died in six months and autopsy showed metastatic cancer.

Our present knowledge of intraepithelial cancer based on sound clinical and pathological observations indicates that cervical cancer can be diagnosed at that stage and that the disease is then curable. An opportunity is thus offered to eradicate this serious and relatively frequent disease by the education of the public as to the value of periodic examinations and by the education of doctors to make the examinations which are necessary for the establishment of the diagnosis.

RICHARD W. TE LINDE.

THE USE OF METHIONINE IN OBSTETRICS

ANIMAL experimentation has shown that nephrosis in combination with widespread liver damage may be caused by severe dietary restrictions. These manifestations were demonstrated to be similar to those found in patients who died due to conditions which produced the clinical picture of the so called hepatorenal syndrome. Certain agents such as chloroform or phosphorus caused marked liver necrosis but this destruction was contingent on the fact that a protein-deficient diet played the predisposing role. Furthermore, experimental work showed that the nutritional necrosis which was found in the liver of these animals had some similarity to the pathological changes of the liver in eclamptic patients. Investigators proved that these conditions in animals could be prevented by the administration of choline plus cystine or by the use of methionine.

Hypoproteinism is a common finding in these conditions. This protein depletion may be the common factor which renders the liver and kidneys more susceptible to hepatotoxic agents. Glycogen has been established as a protective agent to the liver and kidney, but it is only recently that protein has been proved to play an important role in the protection of all tissues of the body. In fact, it is possible for normal liver and kidney function to be maintained only if there is adequate protein intake.

When protein depletion does occur, correction to the proper levels may be facilitated by the intravenous administration of plasma, protein hydrolysates, or by the use of methionine. It is estimated that approximately three grams of methionine is the normal daily intake for an adult. Due to the fact that methionine is an essential amino acid it is not synthesized in the body but must be provided from foods or be given as a supplement to the diet.

Experimental work has shown methionine to be lipotropic in its action. In spite of low protein intake, the administration of this substance prevents fatty infiltration of the liver even in the presence of toxic agents such as phosphorus, carbon tetrachloride or chloroform anesthesia.

It should be realized that experiments in animals do not always coincide with clinical results found in the human, but definite clini-

cal evidence demonstrates that some acute degenerative lesions of vital organs are affected beneficially by the administration of methionine. Recent investigators state that wound healing has been stimulated by its use. In addition, administration of this drug has played a part in prevention of wound disruption in some protein-depleted individuals. Opinions have been expressed both for and against the use of methionine in chronic cirrhotic lesions of the liver, and its value in this regard must be studied further.

Certain obstetrical patients develop complications which cause widespread liver and kidney damage. These conditions have many features relative to protein metabolism and the use of methionine which should be studied. In two recent publications[1] four obstetrical complications which were investigated in this regard were discussed. In patients who showed predisposition to liver damage methionine was given as a supplement to the diet or it was administered intravenously when the patients were too ill to receive it orally. Obstetrical patients suffering from the following complications were treated: patients with severe toxemia, with acute infectious jaundice, with hepatorenal syndrome following surgical shock, and rhesus factor iso-immunized women.

Beneficial results were obtained by the use of methionine in severe pre-eclamptic and eclamptic patients. The improvement was manifested by estimations of liver function, chiefly by means of the cephalin cholesterol test. Clinical improvement was evident by a striking increase in urinary output which was accompanied by diminishing edema in the majority of cases. There was no improvement in those patients who had true chronic nephritis.

[1]MacArthur, J. L. Am. J. Obst. Gyn., 1948, 5: 382; Philpott, N. W. Am. J. Obst. Gyn., 1949, 57: 125.

Methionine and choline were given to pregnant women with acute infectious jaundice. There was no claim made that this procedure would shorten the disease as it had been demonstrated previously that immediate improvement did not occur with this treatment. However, it was given with the surmise that subsequent cirrhotic changes might be prevented. The reported cases are too few and the length of study too brief to permit any conclusions.

Interesting results were obtained in cases of the hepatorenal syndrome which followed surgical or obstetrical shock; all these individuals showed persistent hypotension, anuria, coma, and increasing jaundice. Liver tests denoted impaired liver function in every case. In addition to plasma and whole blood transfusions, intravenous methionine was given apparently with good results.

In the last group of cases there was hemolytic disease of the newborn due to rhesus factor iso-immunization. These cases showed a most convincing effect of methionine as an hepatic protective. Studies were made of pregnant women who showed definite elevation in antibody titrations. Women with the higher antibody levels were placed on methionine every day throughout the remainder of the pregnancy. The remaining cases were used as controls; these patients did not receive the drug but treatment otherwise was identical.

The rationale in giving methionine to the mothers was that if methionine was given in sufficient quantity a good portion would cross the placental barrier into the fetal circulation. Thus it would have a possible protective action on the fetal liver. It was not claimed that methionine could prevent hemolysis of blood but it was given in an attempt to protect the fetal liver which is frequently damaged in this disease. These workers state that it is not

difficult to treat anemia but it is almost impossible to have a baby who is born with a severely damaged liver remain alive and well. The procedure used was to give methionine to the immunized pregnant women throughout the pregnancy. The babies were given smaller doses for the first twelve days of life. Liver function tests which were made on fetal blood showed far less damage when methionine was used. The fetal survival rate also was much improved.

Results have been promising but not conclusive. In the treatment of toxemia and hemolytic disease of the newborn, methionine is a valuable adjunct to other proved types of therapy. The hepatorenal syndrome, which occasionally follows surgical or obstetrical shock, can be treated most efficiently by the combined administration of plasma, whole blood, and intravenous methionine. The problem merits further study.

NEWELL W. PHILPOTT.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

IN the volume, *Surgical Pathology*,[1] the author's aim is to develop a text which may serve as a useful source of information for those general surgeons or members of their allied fields by which they may have ready access to the fundamentals of pathology for active use or for preparation in the various board examinations.

The material has been carefully selected, condensed, and presented without redundant verbiage. The theoretical receives little attention. Debatable subjects are discussed briefly and succinctly. There is a definite objective trend at all times. The writer describes the pathologic changes of each entity, differentiates it from other entities, gives its incidence, quickly incorporates adequate clinical data and avoids prolonged discourse as to "why" it developed. He is more interested in the end result than in the cause. He is more concerned about compiling a proper book on pathology than a diatribe about questionable unproved etiologic agents.

The format is simple. Without hesitation he begins by discussing the skin and ends with the bones and the joints; in other words, he starts on the outside and works his way inward. There is a brief summary of embryology, anatomy, and histology. This reacquaints the reader with ideas which may have become dulled during the passing years.

Although the rare lesions are discussed, the greater amount of space is allotted to the anatomic changes seen most frequently. Both the gross and the microscopic descriptions are complete. Where indicated, there is clinical correlation. The photographs, in black and white, are well selected and appropriate. Further, they are representative of the various lesions.

The print is clear and the paper smooth. There is no glare as one reads. By means of various shades and forms of type, little space is lost in paragraphing and still the various divisions and sections are accentuated.

Emphasis in the bibliography is on the more recent articles and texts of the English speaking countries. In general, there is an extensive amount of information provided by a writer who has had a wide experience in pathology as seen in the operating room.

This reviewer has only one suggestion; to include a section on neuropathology despite the reason for desisting as given in the preface.

The book may be recommended without reservation.

M. C. WHEELOCK.

AN English translation of *Pathologia da gestacao* by Raul Briquet[2] would be welcome. It is a thoroughly modern treatise on pathologic conditions associated with gestation. It differs from most books by presenting practically entirely current opinions and tenets. A glance at the bibliography impresses one with this fact. Seldom is there a work referred to dated before 1930 and references in the early forties are the general rule.

It is a synopsis of diseases of pregnancy, written succinctly, clearly, understandably. Its scope is complete and no subject of importance is left unconsidered. The illustrations are good, well chosen, and technically the book is well done. As far as this reviewer knows there is not a similar work in the English language.

The contents may be divided into four sections. In the preliminary chapters are considerations of the migration of the ovum, nidation, hormones, allergies, and avitaminoses. Subjects not specifically pathologic states of pregnancy are then discussed. Various diseases, 19 in all, are given a chapter each. The more prominent are pulmonary tuberculosis, syphilis, chronic autointoxication, acidosis, alimentation, liver, kidney, blood, and heart diseases, arthropathies, lower genital tract infections, and trauma during gestation.

The specific pathologic states of gestation are treated under such headings as intractable vomiting, hypertension, and eclampsia. The remaining chapters deal with pathologic conditions directly or indirectly associated with the ovum, such as faulty implantation, abortion, intrauterine death, hydatiform mole, and chorioepithelioma. There is appended a chapter on sterilization.

Anyone interested in reviewing pathology of pregnancy will find in this text a complete coverage of the subject set down with a modern touch.

STEPHEN A. ZIEMAN.

IN the book, *The Clinical Management of Varicose Veins*,[3] the author has stressed the important factors in the clinical management and treatment of varicose veins. He agrees with most authorities that

[1] SURGICAL PATHOLOGY. By Peter Herbut, M.D. Philadelphia: Lea & Febiger, 1948.

[2] PATHOLOGIA DA GESTACAO. By Raul Briquet. Sao Paulo: Editora Renascenca, S. A., 1948.

[3] THE CLINICAL MANAGEMENT OF VARICOSE VEINS. By David Woolfolk Barrow, M.D. With foreword by Arthur W. Allen, M.D. New York: Paul B. Hoeber, Inc., 1948.

varicose veins represent a degenerative condition and that the patient will have more varicose veins as time goes on regardless of what method of treatment is used.

The author has discussed very well the subjects of anatomy, physiology, and pathology. Under symptomatology he has discussed in detail the subject of carbon dioxide concentration in the tissues and the association of stasis and edema with the various complications that develop in the lower leg.

In the chapter on examination of the patient he has stressed the importance of the communicating veins. He attributes his good results to careful attention to the communicating veins, and prefers to treat all extensive cases by ligation and stripping and at times with retrograde injection of the sclerosing solution. A high saphenofemoral ligation is followed by thorough stripping and subsequent injection of the remaining veins.

Under "Complications" he expresses the opinion that most complications associated with varicose veins are due to the congestive factor and to the accumulation of toxic products in the tissues. Treatment is directed toward the elimination of this congestive stasis and edema. To accomplish it he carries out a careful ligation of all the perforating veins, injection of the remaining veins which persist, and supportive treatment of the extremity.

Although thrombophlebitis is not discussed as fully as the condition might warrant, this volume can be recommended to any surgeon who treats and who is studying the problem of varicose veins.

H. O. McPheeters.

THE *Textbook of Genito-Urinary Surgery* by Winsbury-White[1] is the most important system of urology since Cabot's *Modern Urology*, the last edition of which appeared in 1936. It is an up-to-date book written by leading British urologists. Chapters have been written by such men as Swift Joly, Terence Millin, Clifford Morson, Jocelyn Swan, and numerous other similarly well known urologic surgeons. Winsbury-White himself has also contributed a number of chapters. The book is complete and suitable not only for the student or part time urologist, but also for the trained, full time urologic surgeon. The chapters on transurethral resection describe the different instruments, the technique of their use, and the results obtained with different methods. Complete chapters are also devoted to the different types of open prostatectomy, including an up-to-the-year discussion by McMillin on his retropubic operation and a discussion on perineal prostatectomy by Winsbury-White. Data on the sulfonamides and antibiotics, which are complete and detailed, are not confined to a single chapter, but are spread through the book and discussed in relation to various different pathologic conditions and surgical procedures.

A number of important, commonly occurring but rarely described, conditions are discussed thoroughly. The chapter on cystitis and associated lesions of the bladder neck is of great value, and the discussion and description of bladder neck polyps and enlarged urethral glands are exceptionally clear cut and instructive. There are numerous illustrations, many in color and all good, depicting surgical technique and pathologic specimens. The clarity and detail of many of the colored drawings of pathologic conditions as seen through the cystoscope are reminiscent of those seen in earlier German urologic texts.

Due to the multiplicity of subjects many conditions and procedures are necessarily dealt with rather briefly, occasionally inadequately. The book is printed with clear type on good paper and is very readable but it is bulky, difficult to handle, and would fit the resting doctor's hand and tilted chair more conveniently if divided into two volumes.

The book is excellent and every urologic surgeon should have it in his library as a source of review and reference text.

A. J. Scholl.

ONE cannot refrain from expressing a word of admiration on the appearance of a beautiful atlas of anatomy[2] coming from a country that was for so long a time under the shadow of war and devastating enemy occupation. The volume includes 512 illustrations, many of them full page and some in color, depicting the osteology, the articulation and the musculature of the human body. There is no descriptive text but each illustration is carefully labelled in accordance with BNA nomenclature to permit accurate and quick recognition of the structure shown.

An interesting innovation is the author's method of indicating muscle position and attachment by showing the muscles in colored diagram overlying the bony structure underneath in black and white.

This volume *Atlas of Human Anatomy* by M. W. Woerdeman should prove exceedingly helpful both to the medical student working in the dissecting room, and to the surgeon refreshing his memory on the details of the operative field he is planning to explore.

Sumner L. Koch.

THE annual publication of the Association for Research in Nervous and Mental Disease, the 27th in the series, represents the proceedings of the Association of the December, 1947, meeting. Unquestionably, this rich volume *The Frontal Lobes*[3] has a front rank position among the other distinguished Research publications of this association.

The book is divided into four sections: biology of the frontal lobes, experimental studies, clinical studies, and frontal lobotomy. In each of these

[1] Textbook of Genito-Urinary Surgery. Edited by H. P. Winsbury-White, M.B., Ch.B., F.R.C.S. (Edin.), F.R.C.S. (Eng.). Baltimore: The Williams & Wilkins Co., 1948.

[2] Atlas of Human Anatomy; Descriptive and Regional. By M. W. Woerdeman, M.D., F.R.N.A.Sc. Vol. 1. Baltimore: The Williams & Wilkins Co., 1948.

[3] The Frontal Lobes. Edited by John F. Fulton, M.D., Charles D. Aring, M.D., and S. Bernard Wortis, M.D. Proceedings of the Association for Research in Nervous and Mental Disease. Vol. 27. Baltimore: The Williams & Wilkins Co., 1948.

parts, the subjects are treated authoritatively by an imposing list of authors whose names represent the top flight laboratory and clinical investigators in neurology in this country at the present time. It is reassuring to know that on the basis of such solid information a rational and safe approach to the clinical problem of the treatment of the psychoses and intractable pain is possible. Regardless of whatever personal feeling the reader may have toward such surgical attack upon the frontal lobes, at least he cannot say that the advocates of such treatment are forcing ahead without sufficient fundamental knowledge of the anatomical, physiological, psychological properties of the frontal lobes. The presentation of the material in this book is, therefore, most timely.

The book is well printed, solidly bound, well illustrated, readable for all the weight of the subject matter, and, as usual in these publications, is supplemented by an extensive cumulative bibliography.

JOHN MARTIN.

THE well printed and beautifully illustrated small volume, *The Modern Management of Gastric and Duodenal Ulcer*,[1] edited by Deller is designed to present to general practitioners, physicians, and surgeons an account of the modern trends in diagnosis and treatment of gastric and duodenal ulcer. In addition to the principal author, there are five collaborators, and, as is to be expected in a book of multiple authorship, this volume is decidedly uneven in quality. The chapters on the applied anatomy and physiology of the stomach and on the pathogenesis of gastric and duodenal ulcer are entirely inadequate and suggest that the authors of these sections are unaware of the large amount of experimental work that has been done in these fields during the past 25 years. While the discussion of the clinical picture of the disease is good, the attempt to explain the cause of ulcer pain reveals that the author of this section is unaware of the extensive studies of W. L. Palmer and of Bonney and Pickering. The section on special investigations and radiology is good and the illustrations are uniformly excellent. By far the best parts of the little book are the sections dealing with surgical therapy. These alone make the volume a valuable addition to the library of both the internist and the surgeon. An excellent description is provided of those surgical procedures that have won a place in the treatment of this disease in the best hospitals and clinics of the world. There is also a good description and discussion of vagotomy and its place in the treatment of duodenal ulcer. The authors point out that whereas the results so far obtained by this newer method of treatment have been almost uniformly good, the period of observation is still too short to permit a final conclusion with respect to its ultimate place.

LESTER R. DRAGSTEDT.

[1] THE MODERN MANAGEMENT OF GASTRIC AND DUODENAL ULCER. Edited by F. Croxon Deller, M.D., M.R.C.P. Baltimore: The Williams and Wilkins Co., 1948.

THE enlarged and revised edition of Bunnell's[2] splendid contribution on the surgery of the hand reflects the progress made in the treatment of wounds and injuries of the hand during the war years and the greatly increased interest that has been aroused in this field of surgery in military and civilian centers. In both of these movements Dr. Bunnell has played a leading and stimulating role, and the entire surgical profession is indebted to him for his contributions to the surgery of the hand and his tireless efforts to work out improved methods of surgical treatment and to make them more widely known.

Many of the men working in military hospitals under Dr. Bunnell's guidance as consulting surgeon have contributed case reports and illustrations to this new edition. In Chapter 5 on Skin and Flexion Contractures, Chapter 6 on Bones, Chapter 7 on Joints, Chapter 10 on Intrinsic Muscles of the Hand and Loss of the Thumb and Chapter 12 on Injuries of the Hand, particularly, are many new diagrams and illustrations, some in color, which illustrate graphically the problems involved, the various methods of treatment advised and the results that have been accomplished.

In Chapter 5 methods of employing the skin of a functionless finger, the tubed flap—at times with utilization of the same flap for the repair of different and separate defects, and the broad "apron" flap from the abdominal wall are illustrated with numerous excellent photographs, many of them generously credited to the men who were carrying out these procedures in widely separated military hospitals. The importance of adequate excision of scar, of wide separation of digits and avoidance of binding scars at the webs are repeatedly emphasized both in the application of pedunculated flaps and of free grafts.

Chapter 6 on Bones has been enlarged from 12 to 36 pages. A number of methods of restoring the bony framework injured by accident or as a result of gunshot wounds, are described with the aid of diagrams, photographs and x-ray films. These methods include the use of cancellous and cortical bone grafts, substitution of a metatarsal for a metacarpal bone, shifting of an uninjured metacarpal to replace an adjacent bone and the use of multiple metal pins or Kirschner wires to help provide fixation and immobilization. Iliac bone, rib grafts, tibial grafts have all been used successfully and a number of ingenious methods for employing them to advantage are indicated in diagrammatic sketches.

Chapter 10 on Intrinsic Muscles of the Hand and Loss of the Thumb has also been enlarged by 30 pages, and a number of complicated problems are discussed with well illustrated examples. Fowler's method of repair of injured extensor tendons, methods of securing abduction of the index finger following loss or injury of the first dorsal interosseus, of securing flexion of the proximal phalanges in patients with ulnar and median palsy, and of securing rotation and adduction of the thumb are considered at length,

[2] SURGERY OF THE HAND. By Sterling Bunnell, M.D. 2d ed. Philadelphia, London and Montreal: J. H. Lippincott, Co., 1948.

and with clear, well conceived diagrams of operative procedures and numerous illustrations of the results obtained. A considerable amount of new material has also been added on methods of providing a substitute for the lost thumb.

The first edition of Bunnell's *Surgery of the Hand* was an outstanding contribution to surgical literature. In the second edition the author has added new material and new concepts of repairing the injured hand that should lead to definite improvement and still greater interest in the surgical management of injured hands. The entire surgical profession is indebted to him for this comprehensive study of an important and often neglected field of surgery.

SUMNER L. KOCH.

THE book *Practical Bacteriology, Hematology, and Parasitology*[1] needs no introduction to laboratory workers and physicians as its usefulness has been well demonstrated by 9 revisions since its first appearance in 1909. Each new edition has allotted more space to the interpretation and diagnostic significance of various laboratory procedures. The greatest emphasis has been placed on bacteriology, hematology, and parasitology as the title indicates; however, all types of laboratory work are included.

Part 1, the section on bacteriology, has been almost entirely rewritten and brought up to date by Dr. Branham who replaces Dr. Mildred Clark Clough as coeditor. It is impossible to list all the additions, but a few may be mentioned, such as newer laboratory methods of diagnosing diseases due to Rickettsia, filterable viruses, and fungi. The chapter on mycology is well illustrated and includes a section on antibiotics. The methods of assay of penicillin in blood and the determination of the sensitivity of the organism to penicillin are given in the chapter on staining methods and special procedures.

Part 2, the section on hematology, has been revised less extensively than the others. Methods for the determination of prothrombin and the Rh-Hr factors have been added, as well as the significance of the Rh factor in erythroblastosis fetalis.

Part 3, the section on parasitology, has been rewritten and a great deal of new material added, including new work on malaria, schistosomiasis, filariasis, DDT, and arthropod transmission of disease. There are many new illustrations; especially good are those giving the life cycle of the various parasites.

Part 4, entitled "Clinical and Pathological Examination of Body Fluids and Organs," covers a large number of subjects in a relatively small space. It includes methods for the examination of urine, feces, sputum, gastric contents, cerebrospinal fluid, and the chemical examination of blood. Chapter 44 of this section on vitamins as specific food factors has a brief bibliography appended. The last section of the appendix lists, according to diseases, laboratory procedures useful in their diagnosis.

The editors, as well as the many contributors to this book, are to be congratulated on keeping this edition up to the high standards of the previous ones. This book for the many years of its existence has been a constant source of information to laboratory workers. It contains material not available in other textbooks. This edition is full of the latest work on subjects vital to the diagnosis of disease by laboratory methods.

OPAL E. HEPLER.

THE book *Preoperative and Postoperative Care of Surgical Patients*[2] by Hugh C. Ilgenfritz has covered rather thoroughly the major developments of the war and of the past decade which have contributed most to the pronounced reduction in mortality and morbidity in surgical patients. The importance of the proper attention to nutrition, fluid and electrolyte balance, and whole blood requirements before, during, and after surgery has been stressed throughout the book.

Chapters on fluid and electrolyte balance, and metabolism and nutrition constitute a concise but informative review of these important subjects.

Shock and blood transfusion are considered in separate chapters. While most of the theories as to the etiology of shock are discussed, evidence that whole blood loss is the prime etiological factor and that whole blood replacement is the chief weapon in combating shock is emphasized. Plasma and plasma substitutes are discussed, and their limitations as blood substitutes are well outlined.

Sedative medications and choice of anesthetic agent are discussed in one chapter. There are chapters on general preoperative and postoperative measures.

Other chapters deal with systemic complicating factors, organic diseases, chemotherapeutic and antibiotic drugs, major and minor postoperative complications, intestinal obstruction and peritonitis, care of the wound, and burns. The latter third of the book is devoted to preoperative and postoperative care in surgery of the chest, the stomach, the small intestine and appendix, the large bowel, the biliary tract, the thyroid, the extremity, and the female pelvis.

In his presentation of all these subjects, the author has not limited himself to the discussion of one recommended procedure. Different methods of management are evaluated. All sides of controversial issues are presented.

Considerable attention has been given to detail, essential in the preoperative and postoperative care of surgical patients. Essential laboratory tests are described, so that with the necessary material available these tests can be performed without other reference data.

[1] PRACTICAL BACTERIOLOGY, HEMATOLOGY, AND PARASITOLOGY. By E. R. Stitt, M.D., Ph.D., Sc.D., LL.D., Paul W. Clough, M.D., Sara E. Branham, M.D., Ph.D., Sc.D., and contributors. 10th ed. Philadelphia: The Blakiston Co., 1948.

[2] PREOPERATIVE AND POSTOPERATIVE CARE OF SURGICAL PATIENTS. By Hugh C. Ilgenfritz, A.B., M.D., F.A.C.S. St. Louis: The C. V. Mosby Co., 1948.

There is little in the book which might be criticized. Cardiorespiratory embarrassment, peritoneal contamination, and sepsis are not discussed as etiological factors in shock. Perhaps not enough consideration has been given to the management of the patient who develops anuria following blood transfusion reaction, crush syndrome, and traumatic shock. The exceeding importance of limiting fluids once the anuria is known to exist, so as not to overload the circulation, is not mentioned. The discussion of gas gangrene does not include diagnostic criteria for the differentiation of true gas gangrene or clostridial myositis from anaerobic cellulitis, which were outlined by MacLennen, and later by Jergesen and Simeone.

These minor criticisms do not detract from the general worth of the book as a reference text on preoperative and postoperative care. The author has told not only what to do, but how to do it and why it should be done. The book can be recommended for interns, residents, and all practicing surgeons.

HOWARD E. SNYDER.

THE book *Successful Marriage*[1] is a symposium of discussions dealing with every aspect of modern marriage. The 515 page book is written by a panel of physicians, sociologists, and psychologists, each an expert in his field. Dr. Fishbein and Dr. Burgess have carefully correlated the material to present an outstanding treatise on marital relationships of today. While the book is written primarily for the laity, the physician who may be called upon to act as a marriage counselor will do well to familiarize himself with its contents and recommend it as authoritative reading to those who consult him about marital problems.

The book is divided into 5 parts. Part 1, entitled "Preparation for Marriage," consists of 6 chapters encompassing important advice such as the determination of true love and the wise choice of a mate. A thorough understanding of these subjects before marriage is indeed vital to marital success.

Part 2, "The Marriage," is concerned chiefly with anatomical, physiological, and psychological factors in marital adjustment not generally available to the newlywed. Sexual technique and adjustment is frankly discussed and easily comprehended. A chapter on home management and finance is filled with excellent suggestions. The discourse on marital maladjustments due to psychological factors should be of great value to perplexed marital partners. It stresses the importance of seeking psychiatric advice as soon as such advice is needed and at a time when a remedy will be most easily effected. The inclusion here of an excellent chapter on miscarriage and abortion seems to be incongruous, for it belongs more correctly with the subject following.

Part 3, "Conception, Pregnancy, and Childbirth" deals with heredity, facts on pregnancy, mechanism of childbirth, and economic problems attendant on parenthood. There is an excellent chapter on factors favoring fertility and the basal temperature graph as an aid to conception. Contraceptive methods are also discussed.

Part 4, "The Child and the Family," includes 9 chapters pertaining to such subjects as physical and psychological growth of the child, sex problems and education, and adolescent preparation for successful marriage. Since the presence of children is a dominant factor in marital happiness, the benefits of adoption are cited in instances where natural childbearing is impossible. The chapter on parent-child relationships is outstanding.

Part 5, "Social Problems of Sex and Marriage," concerns itself with social subjects, a few of which are of questionable value in a book on marital success. The chapter on prostitution in the United States is one of these. Since many groups are reluctant to accept the dissolving of marriage as a solution to marital problems, the chapter on divorce is bound to be controversial.

In general, the book is frank, thorough, and exceedingly well written. Practically applied, the suggestions and advice set forth within this book should tend to make available the attainment of a completely happy marriage. THEODORE J. MORRIS.

FOR a practitioner with any interest in anesthesia, the book *Pediatric Anesthesia*[2] will certainly be a well used addition to his library. The problems of pediatric anesthesia are completely discussed from the general requirements for handling children, through the preanesthetic consultation and premedication, to an exhaustive, clear, and stepwise discussion of techniques involved in pediatric anesthesia, and finally to the postoperative care with the possible complications, how to avoid them, and their treatment if necessary.

A chapter involving the special physiology of the infant is included in an effort to emphasize the particular nature of the responses of the child and new born to the administration of anesthetic drugs.

The authors are detailed in their explanations. As they state, ". . . the specialist has reached eminence by mastering detail." They leave no important consideration to chance.

In the chapter concerning inhalation anesthesia, the choice of agent, methods and techniques generally are reviewed. The endotracheal section is of practical importance to adult anesthesia as well, since it lucidly explains methods which are certainly valid in all usage of these devices. The steps of intubation, if followed, will certainly facilitate smooth performance of this maneuver. The use of intravenous anesthetic agents in children is discussed, and particularly valuable in this chapter is the section concerning the use of curare both as to the surgical or major relaxation effect and its aid to the anesthesiologist in reducing the induction period for

[1] SUCCESSFUL MARRIAGE. Edited by Morris Fishbein, M.D., and Ernest W. Burgess, Ph.D. Garden City, N.Y.: Doubleday and Co., Inc., 1948.

[2] PEDIATRIC ANESTHESIA. By M. Digby Leigh, M.D., and M. Kathleen Belton, M.D. New York: The Macmillan Co., 1948.

intubation. The importance of adequate curarization is just as important in children as in adults. The most lengthy chapter of the book presents a dissertation of anesthetic agents and techniques which affords an excellent guide, particularly for the student. This chapter lists the more common surgical procedures and discusses the several anesthetic methods suitable for them. It is not dogmatic, but explains the reasons for such choice and includes examples of risk involved.

This volume does not introduce any spectacular new considerations, but it does present the entire picture of the field of pediatric anesthesia and reemphasizes the use of skill and judgment in the application of anesthetic drugs to any patient.

FRANCIS M. SELLERS.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

HANDBOOK OF SURGERY. By Eric C. Mekie, M.B., Ch.B., F.R.C.S. (Edin.), and Ian Mackenzie, M.B.E., M.B., Ch.B., F.R.C.S. (Edin.). With a Foreword by the late Sir John Fraser, Bart., M.C., M.D., Ch.M., F.R.C.S. (Edin.). 2d ed. Baltimore: The Williams & Wilkins Co., 1949.

A SURGEON'S GUIDE TO LOCAL ANAESTHESIA; A MANUAL OF SCHOCKLESS SURGERY. By C. E. Corlette, M.D., Ch.M. (Syd.), F.R.A.C.S. Baltimore: The Williams & Wilkins Co., 1948.

OPERATIVE SURGERY. By Frederick C. Hill, B.A., M.S. (Surg.), M.D. Foreword by Charles W. Mayo, B.A., M.S. (Surg.), M.D. New York: Oxford University Press, 1949.

CARDIAC CATHETERIZATION IN CONGENITAL HEART DISEASE; A CLINICAL AND PHYSIOLOGICAL STUDY IN INFANTS AND CHILDREN. By Andre Cournand, M.D., Janet S. Baldwin, M.D., and Aaron Himmelstein, M.D. New York: The Commonwealth Fund, 1949.

ATLAS OF ORAL AND FACIAL LESIONS AND COLOR FILM LIBRARY. By Ralph Howard Brodsky, D.M.D. Baltimore: The Williams & Wilkins Co., 1948.

DIE GEBURTSHILFLICHEN OPERATIONEN; IHRE AUSFÜHRUNG UND ANWENDUNG. EIN LEHRBUCH FUER STUDIERENDE UND GEBRAUCHSBUCH FUER ARZTE. By Prof. Dr. Med. Heinrich Martius. Stuttgart: Georg Thieme, Verlag, 1948.

PATHOLOGISCHE PHYSIOLOGIE DER FRISCHEN, GESCHLOSSENEN HIRNVERLETZUNG, INSBESONDERE DER HIRNERSCHUTTERUNG; KLINISCHE, ANATOMISCHE UND EXPERIMENTELLE BEFUNDE. By R. Wanke. Stuttgart: Georg Thieme Verlag, 1948.

LEHRBUCH DER GEBURTSHILFE. By Prof. Dr. Med. Heinrich Martius. Assisted by Prof. Dr. Med. Werner Bickenbach, Prof. Dr. Med. Kurt Nordmeyer, and Kathe Droysen. Vol. 1: PHYSIOLOGIE. Vol. 2: PATHOLOGIE. Stuttgart: Georg Thieme Verlag, 1948.

TECHNIQUES DE CHIRURGIE PELVIENNE. By R. Michel-Bechet. Paris: G. Doin & Cie, 1948.

NOUVELLE PRATIQUE CHIRURGICALE ILLUSTRÉE. Jean Quenu, Directeur. Vol. 11. Paris: G. Doin & Cie, 1948.

TECHNIQUE DE LA CHIRURGIE DU SYMPATHIQUE ET DE SES INFILTRATIONS. By O. Lambret, P. Razemon, and P. Decoulx. 3d enl. rev. ed. Paris: G. Doin & Cie, 1948.

VETERANS ADMINISTRATION TECHNICAL BULLETINS; Series 10. Vol. 2. Washington, D.C.: Veterans Administration, 1949.

TRANSACTIONS OF THE THIRD AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY. Municipal Auditorium, St. Louis, Missouri, September 8 to 12, 1947. Edited by George W. Kosmak, M.D., and Robert N. Rutherford, M.D. Portland, Oregon: The Western Journal of Surgery Publishing Co., 1948.

CHILD HEALTH SERVICES AND PEDIATRIC EDUCATION: Report of the Committee for the Study of Child Health Services, The Academy of Pediatrics with the cooperation of the United States Public Health Service and the United States Children's Bureau. New York: The Commonwealth Fund, 1949.

CARE OF THE SURGICAL PATIENT; INCLUDING PATHOLOGIC PHYSIOLOGY AND PRINCIPLES OF DIAGNOSIS AND TREATMENT. By Jacob Fine, M.D. Philadelphia and London: W. B. Saunders Co., 1949.

A PRIMER OF ELECTROCARDIOGRAPHY. By George E. Burch, M.D., F.A.C.P., and Travis Winsor, M.D., F.A.C.P. 2d ed. Philadelphia: Lea & Febiger, 1949.

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PULMONARY TUBERCULOSIS; PATHOLOGY, DIAGNOSIS, MANAGEMENT AND PREVENTION. By Walter Pagel, M.D., F. A. H. Simmonds, M.A., M.D., D.P.H., N. Macdonald, M.B., M.R.C.P.Ed., and L. Fatti, F.R.C.S. Revised and partly rewritten 2d ed. London, New York, and Toronto: Geoffrey Cumberlege; Oxford University Press, 1948.

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CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

DALLAS B. PHEMISTER, Chicago, *President*
FREDERICK A. COLLER, Ann Arbor, Michigan, *President-Elect*

PRELIMINARY PROGRAM FOR THE 35th CLINICAL CONGRESS THE STEVENS, CHICAGO, OCTOBER 17 to 21, 1949

THE thirty-fifth Clinical Congress of the American College of Surgeons will be held in Chicago from October 17 to 21, 1949, with hotel headquarters at The Stevens. The Clinical Congress, in addition to its usual five-day program, will be host to the Sixth Inter-American Congress of Surgery, which will open on Friday morning, October 21, and hold sessions through Sunday, October 23. The plans for the Inter-American Congress are described in a separate article.

Some twenty hospitals in the Chicago area which are approved for graduate training in surgery will participate in the clinical program. Operative and nonoperative clinics will be held in the hospitals each day in general surgery, obstetrics and gynecology, fractures, orthopedic surgery, thoracic surgery, neurosurgery, genitourinary surgery, and ophthalmology and otorhinolaryngology. The schedule of clinics will be published in a *Daily Clinical Bulletin* which will be issued each day during the Congress.

Arrangements are under way to telecast operations to the hotel from one or more of the hospitals. The successful demonstrations of television at the Clinical Congress in New York in 1947, and at the Clinical Congress in Los Angeles in 1948, make it highly desirable to continue the use of this medium. Television has proved itself to be a superlative instrument to further the "Show me" purpose which was the main incentive for the founding of the Clinical Congress in 1910, three years before the American College of Surgeons was organized.

The program of meetings at the headquarters hotel will be varied and comprehensive. The opening session on Monday morning, October 17, will be a general assembly for both surgeons and hospital personnel. Scientific sessions, official meetings, and hospital conferences will follow during the five days, and many will undoubtedly wish to remain for the sessions of the Sixth Inter-American Congress of Surgery on Saturday and Sunday. Delegates and visitors to the latter meeting will likewise be welcome at clinics and scientific sessions of the Clinical Congress.

PRESIDENTIAL MEETING

The opening evening session of the Clinical Congress will be devoted to the Presidential Meeting, at which the officers-elect, consisting of Dr. Frederick A. Coller of Ann Arbor, president, Dr. Donald G. Tollefson of Los Angeles, first Vice-president, and Dr. Robert M. Moore of Galveston, second vice-president, will be installed. Dr. Dallas B. Phemister of Chicago, outgoing president, will preside and will deliver the Presidential Address. The fourth Martin Memorial Lecture will be delivered by Sir James R. Learmonth, Edinburgh, whose subject will be "Collateral Circulations, Natural and Artificial."

CONVOCATION

The annual Convocation will be held on the final evening Friday. The formal initiation ceremonies for the new Fellows will be a colorful feature of the occasion. The Fellowship Address will be given by Lord Webb-Johnson of London, President of the Royal College of Surgeons.

EVENING SCIENTIFIC SESSIONS— GENERAL SURGERY

The program and speakers for the Tuesday evening general surgery session will be as follows:

Acute Surgical Emergencies in Gynecology and Obstetrics

General Introduction. NEWELL W. PHILPOTT, M.D., F.A.C.S., Montreal.

Tubal Pregnancy, Its Diagnosis and Treatment. LEWIS C. SCHEFFEY, M.D., Philadelphia.

Pelvic Peritonitis Occurring in the Obstetrical or Gynecological Patient. FRANK GLENN, M.D., F.A.C.S., New York.

Emergency Cesarean Section. WILLIAM E. STUDDIFORD, M.D., F.A.C.S., New York.

The program and speakers for the Wednesday evening general surgery session will be as follows:

Fracture Oration

Blood Coagulation and the use of Anticoagulants:

The Significance of Different Methods for Prothrombin Estimation and their Relative Values. JOHN H. OLWIN, M.D., Chicago.

Studies on Antithrombin and Etiologic Factors in Phlebothrombosis. JOHN H. KAY M.D., New Orleans.

A Further Report on Dicumarol Prophylaxis against Venous Thrombosis in Women Undergoing Surgery. GEORGE VAN S. SMITH, M.D., F.A.C.S., Brookline, Massachusetts.

The program and speakers for the Thursday evening general surgery session will be as follows:

Chemotherapy in Malignant Neoplastic Disease. CARL V. MOORE, M.D., St. Louis.

Hormone Therapy of Cancer. CHARLES B. HUGGINS, M.D., Chicago.

The Use of Radioactive Iodine in Studying the Pathologic Physiology of Thyroid Cancer. RULON W. RAWSON, M.D., New York.

What We have Learned from Isotopes Concerning Depletion and Repair in Surgical Patients. FRANCIS D. MOORE, M.D., F.A.C.S., Boston.

GENERAL SURGERY PANEL DISCUSSIONS

General surgery panel discussions will be held on Monday, Tuesday, and Wednesday afternoons, from 1:30 to 3:00 and from 3:30 to 5:00 o'clock. The subjects and names of moderators follow:

Monday—1:30 to 3:00 p.m.

Surgical Lesions of the Breast. GEORGE G. FINNEY, M.D., F.A.C.S., Baltimore.

3:30 to 5:00 p.m.

Fractures of the Skull. ELDRIDGE H. CAMPBELL, M.D., F.A.C.S., Albany.

Tuesday—1:30 to 3:00 p.m.

Massive Upper Abdominal Hemorrhage. JOHN H. MULHOLLAND, M.D., F.A.C.S., New York.

3:30 to 5:00 p.m.

New Surgical Technique in Drug Treated Infections. S. CHAMP LYONS, M.D., F.A.C.S., New Orleans.

Wednesday—1:30 to 3:00 p.m.

The Management of Acute Emergencies Occurring During Operations. I. MIMS GAGE, M.D., F.A.C.S., New Orleans.

3:30 to 5:00 p.m.

Preoperative and Postoperative Care and Anesthesia for Infants. THOMAS H. LANMAN, M.D., F.A.C.S., Boston.

SPECIALTY SESSIONS

Plans will be announced later for the sessions in ophthalmology, otorhinolaryngology, orthopedic surgery, plastic surgery, urology, thoracic surgery, neurological surgery, and obstetrics and gynecology. Friday afternoon will be devoted to panel discussions in the surgical specialties, but a definite schedule has not yet been completed for other sessions.

FORUM ON FUNDAMENTAL SURGICAL PROBLEMS

The Forum on Fundamental Surgical Problems will be held on Tuesday through Friday mornings, and from 1:30 to 3:00 o'clock on Thursday afternoon. Brief reports of original clinical and experimental observations relating to the broad aspects of surgery and the surgical specialties will be presented, under the general direction of Dr. Owen H. Wangensteen, chairman of the committee, Forum on Fundamental Surgical Problems.

HOSPITAL CONFERENCES

The twenty-eighth Hospital Standardization Conference will be held during the first four days of the Clinical Congress. Its opening meeting will constitute the first formal session of the Clinical Congress and will be for both surgeons and hospital representatives. Dr. Dallas B. Phemister, president of the College, will preside.

Hospital administrators, trustees, members of medical staffs, nurses, technicians, dietitians, and heads of the various hospital departments and their personnel, are invited to participate in the discussions at the hospital conferences which will be directed by leading authorities in the hospital field in the United States and Canada. The program will include formal sessions, panel discussions, round table conferences, symposia, and forums.

MEDICAL MOTION PICTURES

The showing of medical motion pictures each day will again be a popular feature of the Clinical Congress. The latest available films on surgery and related subjects will be presented. Special

showings will be arranged of medical motion pictures in the fields of ophthalmology and otorhinolaryngology. Both sound and silent films will be shown, all of which will have been approved by the Committee on Motion Pictures. Some of the newer medical motion pictures which are now under production will be completed by the time of the Clinical Congress.

COMMITTEE ON ARRANGEMENTS

The Chicago Committee on Arrangements for the Clinical Congress is actively at work on arrangements for the program. The membership follows:

Warren H. Cole, M.D., F.A.C.S., Chairman
Michael L. Mason, M.D., F.A.C.S., Secretary
William E. Adams, M.D., F.A.C.S.
Fremont A. Chandler, M.D., F.A.C.S.
Edward H. Christofferson, M.D., F.A.C.S.
Vernon C. David, M.D., F.A.C.S.
M. Edward Davis, M.D., F.A.C.S.
Loyal Davis, M.D., F.A.C.S.
Lester R. Dragstedt, M.D., F.A.C.S.
Paul W. Greeley, M.D., F.A.C.S.
Paul H. Holinger, M.D., F.A.C.S.
Sumner L. Koch, M.D., F.A.C.S.
Herman L. Kretschmer, M.D., F.A.C.S.
Walter G. Maddock, M.D., F.A.C.S.
Foster L. McMillan, M.D., F.A.C.S.
Karl A. Meyer, M.D., F.A.C.S.
Harry A. Oberhelman, M.D., F.A.C.S.
Dallas B. Phemister, M.D., F.A.C.S.
Willis J. Potts, M.D., F.A.C.S.
Charles B. Puestow, M.D., F.A.C.S.
Herbert E. Schmitz, M.D., F.A.C.S.
Derrick T. Vail, M.D., F.A.C.S.

The Clinical Congress general committee which operates under the Administrative Board of the College, consists of Dr. Malcolm T. MacEachern, chairman, Miss Eleanor K. Grimm, secretary, Doctors Bowman C. Crowell, Charles F. Branch, George H. Miller and H. Prather Saunders, and Mr. Edward G. Sandrok, Mr. James S. Shannon, and Miss Laura G. Jackson.

The Clinical Congress Committee on Programs consists of Dr. Frederick A. Coller, chairman, and Doctors Henry W. Cave, Evarts A. Graham, and Alton Ochsner.

The Advisory Committee on Programs consists of Dr. George H. Miller, chairman, and Doctors Warren Cole, Sumner Koch, Michael Mason, Charles Puestow, Bowman C. Crowell, H. Prather Saunders, Charles F. Branch, and Malcolm T. MacEachern.

TECHNICAL AND SCIENTIFIC EXHIBITION

The Technical and Scientific Exhibits will be held in the Exhibition Hall on the lower level of The Stevens. Leading manufacturers of surgical instruments, x-ray apparatus, sterilizers, operating room lights, ligatures, dressings, hospital apparatus and supplies of all kinds, and pharmaceuticals, and publishers of medical books will be represented.

ADVANCE REGISTRATION

Surgeons who wish to attend the Congress should register in advance. Advance registration will greatly expedite the procedure of registering. No registration fee will be charged Fellows whose dues are paid to December 31, 1948. For endorsed Junior and Senior Candidates, the fee will be $5.00. Non-Fellows who after individual consideration are permitted to register, will pay a fee of $10.00. No registration fee will be required of initiates of the class of 1949.

HOTEL RESERVATIONS

It is desirable to make hotel reservations as early as possible. In making these, communications should be addressed to the Convention Housing Bureau, 105 West Adams Street, Chicago, stating that you will be attending the Clinical Congress of the American College of Surgeons. All hotel reservations, both for surgeons and hospital representatives, are to clear through this Bureau. No correspondence should be sent directly to the hotels. A form for reservations was enclosed in the letter recently sent to Fellows. Choice of hotels may be designated.

A list of the major hotels follows:

CHICAGO HOTELS

Bismarck, 171 W. Randolph Street
Blackstone, Michigan Avenue at 7th Street
Congress, 500 S. Michigan Avenue
Drake, Michigan and Lake Shore Drive
Harrison, 57 E. Harrison Street
Lake Shore Drive, 181 Lake Shore Drive
LaSalle, 10 N. LaSalle Street
Morrison, 79 W. Madison Street
Palmer House, 15 E. Monroe Street
Sheraton, 505 N. Michigan Avenue
Sherman, 106 W. Randolph Street
Stevens, 720 S. Michigan Avenue

SIXTH INTER-AMERICAN CONGRESS OF SURGERY

THE thirty-fifth Clinical Congress of the American College of Surgeons will be host to the sixth Inter-American Congress of Surgery when it convenes in Chicago on October 21, 22, and 23. On its first day it will overlap with the Clinical Congress. The delegates and visitors from Latin American countries will be welcome to attend all sessions of the Clinical Congress, and the operative clinics at the hospitals.

The American College of Surgeons joined the Association of Inter-American Congresses of Surgery by vote of the Board of Regents on June 27, 1944. This action was preceded by an invitation from Dr. Luis Vargas Salcedo of Santiago, Chile, dated July 21, 1942, to send two delegates as guests of honor to the first Inter-American Congress of Surgery in Santiago, held November 14 to 19, 1942. Dr. Leo Eloesser attended as delegate, and it was upon his enthusiastic recommendation that the College accepted the invitation to join. He also attended the second Congress held in Buenos Aires, October 10 to 15, 1943. Dr. Alton Ochsner was delegate to the third Congress, held in Rio de Janeiro from September 6 to 15, 1947. The fifth Congress was held in La Paz, Bolivia, October 17 to 21, 1948, with Dr. E. Payne Palmer of Phoenix and Dr. Hu Crim Myers of Philippi, West Virginia, as delegates and co-relators.

The surgical societies of the following countries, in addition to the United States, are members of the Association of Inter-American Congresses of Surgery: Argentina, Brazil, Bolivia, Chile, Cuba, Ecuador, Mexico, Panama, Paraguay, Peru, and Uruguay. Dr. Arnaldo Caviglia of Buenos Aires is the Secretary-General.

A preliminary outline of the program for the Sixth Inter-American Congress of Surgery follows:

Friday morning, October 21

Inaugural Ceremony

Friday afternoon, October 21

Delegates may attend the specialty panels of the Clinical Congress

Saturday morning, October 22

Main Theme: Acute Craniocerebral Trauma
Relator: E. Jefferson Browder, M.D., F.A.C.S., Brooklyn
Co-relators: To be appointed by each country

Saturday afternoon, October 22

Main Theme: Treatment of Injuries in the Region of the Ankle with Complications and Sequelae
Relator: Harrison L. McLaughlin, M.D., F.A.C.S., New York
Co-relators: To be appointed by each country

Saturday evening, October 22

Official Banquet

Sunday morning, October 23

Business Session

Sunday afternoon, October 23

Main Theme: Pulmonary Carcinoma
Relator: E. Evarts Graham, M.D., F.A.C.S., St. Louis
Co-relators: To be appointed by each country

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SURGERY Gynecology and Obstetrics

With International Abstracts of Surgery

VOLUME 88 June, 1949 NUMBER 6

Meat and the Management Of Macrocytic Anemias

A recent clinical study* on the efficacy of vitamin B_{12} in macrocytic anemias emphasizes the value of a diet high in complete protein in the general management of these conditions.

In addition to specific antianemia therapy "a diet rich in animal protein" is recommended as one of the principles of treatment in pernicious and related macrocytic anemias.

Meat deserves a prominent place in the dietary of these anemias. It is an outstanding source of complete protein, providing all the amino acids essential for blood formation and tissue repair. In addition to its notably high content of complete protein, meat is one of man's best natural sources of B-complex vitamins and iron.

The excellent digestibility of meat makes possible its use twice or more times daily when required by dietary demands.

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*Spies, T. D.; Suarez, R. M.; Lopez, G. G.; Milanes, F.; Stone, R. E.; Toca, R. L.; Aramburu, T., and Kartus, S.: Tentative Appraisal of Vitamin B_{12} as a Therapeutic Agent, J.A.M.A. *139*:521 (Feb. 19) 1949.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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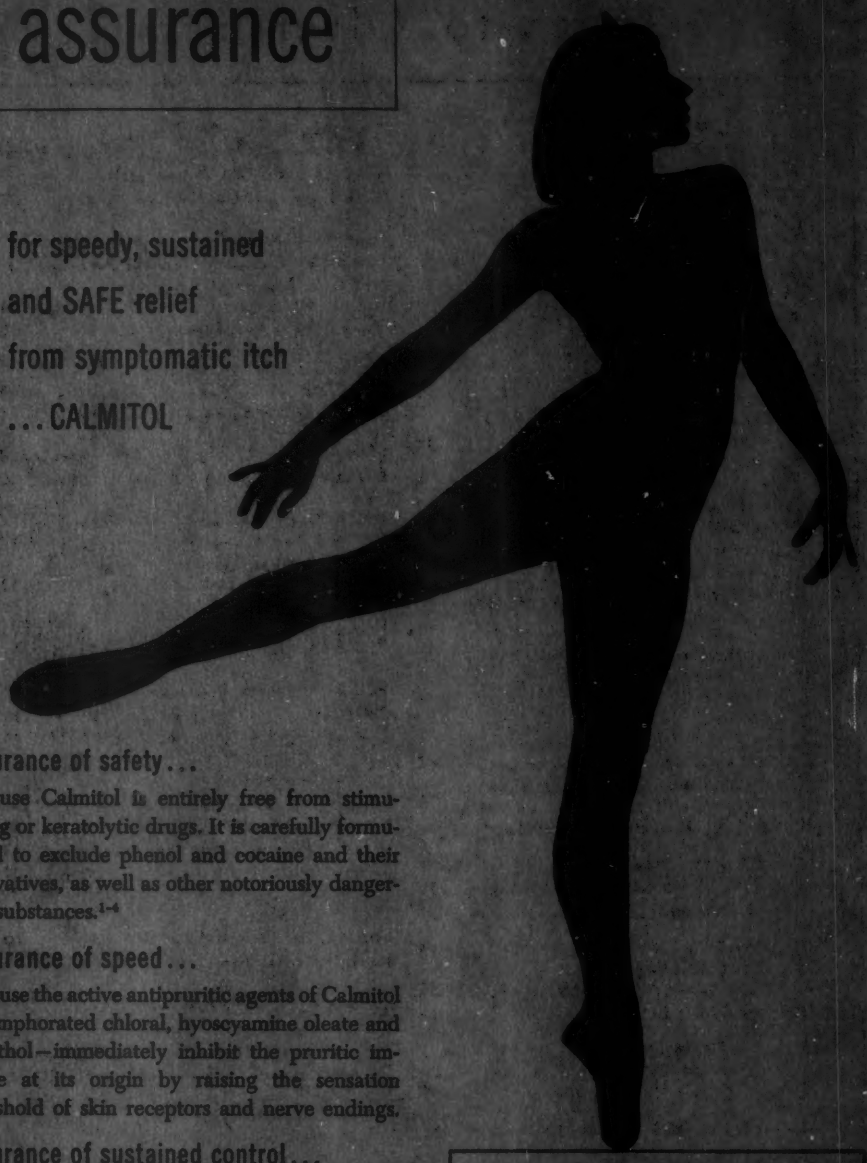

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1. Underwood, G. B., and Gaul, L. E.: J.A.M.A. 136:570, 1948. 2. Underwood, G. B.; Gaul, L. E.; Collins, E., and Mosby, M.: J.A.M.A. 130:249, 1946. 3. Andrews, G. C.: Diseases of the Skin, Philadelphia, W. B. Saunders Co., 1946. 4. Gaul, L. E.: J.A.M.A. 127:439, 1945.

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